In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. 17-642V
Filed: June 24, 2022
PUBLISHED

ELIZABETH DOLES,

Petitioner,

v.

SECRETARY OF HEALTH AND HUMAN SERVICES,

Respondent.

Special Master Horner

Decision on Remand; Multiple Sclerosis ("MS"); Significant Aggravation; Tetanus Diphtheria acellular Pertussis ("Tdap") Vaccine; Polio Vaccine

Joseph Alexander Vuckovich, Maglio Christopher & Toale, PA, Washington, DC, for petitioner.
Catherine Elizabeth Stolar, U.S. Department of Justice, Washington, DC, for respondent.

DECISION ON REMAND[1]

On May 16, 2017, petitioner filed a petition under the National Childhood Vaccine Injury Act, 42 U.S.C. § 300aa-10-34 (2012)[2], alleging that she suffered acute disseminated encephalomyelitis ("ADEM") as a result of her receipt of the polio vaccination on April 4, 2016, and/or a tetanus, diphtheria, and pertussis ("Tdap") vaccination on April 22, 2016. (ECF No. 1.) On July 5, 2019, petitioner amended her petition, now alleging that the vaccinations she received in April of 2016 caused her central nervous system ("CNS") demyelination best categorized as multiple sclerosis ("MS"). (ECF No. 44.) Petitioner alleged that her condition was caused, or alternatively significantly aggravated, by her vaccinations. (*Id*. at 2-3.)

[1] Because this decision contains a reasoned explanation for the special master's action in this case, it will be posted on the United States Court of Federal Claims' website in accordance with the E-Government Act of 2002. *See* 44 U.S.C. § 3501 note (2012) (Federal Management and Promotion of Electronic Government Services). **This means the decision will be available to anyone with access to the Internet**. In accordance with Vaccine Rule 18(b), petitioner has 14 days to identify and move to redact medical or other information the disclosure of which would constitute an unwarranted invasion of privacy. If the special master, upon review, agrees that the identified material fits within this definition, it will be redacted from public access.

[2] All references to "§ 300aa" below refer to the relevant section of the Vaccine Act at 42 U.S.C. § 300aa-10-34.

Initially, I issued a ruling on entitlement finding petitioner entitled to compensation for a significant aggravation of her pre-existing MS. Respondent moved for review of that determination and the Court of Federal Claims subsequently granted the motion, finding error both with respect to procedure and consideration of the record evidence. The Court remanded the case for further proceedings and for a determination of entitlement under the correct legal and scientific standards. The instant decision results from that remand. For the reasons set forth below I find that petitioner is entitled to compensation.

I. Applicable Statutory Scheme

Under the National Vaccine Injury Compensation Program, compensation awards are made to individuals who have suffered injuries after receiving vaccines. In general, to gain an award, a petitioner must make a number of factual demonstrations, including showing that an individual received a vaccination covered by the statute; received it in the United States; suffered a serious, long-standing injury; and has received no previous award or settlement on account of the injury. Finally – and the key question in most cases under the Program – the petitioner must also establish a *causal link* between the vaccination and the injury. In some cases, the petitioner may simply demonstrate the occurrence of what has been called a "Table Injury." That is, it may be shown that the vaccine recipient suffered an injury of the type enumerated in the "Vaccine Injury Table," corresponding to the vaccination in question, within an applicable time period following the vaccination also specified in the Table. If so, the Table Injury is presumed to have been caused by the vaccination, and the petitioner is automatically entitled to compensation, unless it is affirmatively shown that the injury was caused by some factor other than the vaccination. § 300aa-13(a)(1)(A); § 300 aa-11(c)(1)(C)(i); § 300aa-14(a); § 300aa-13(a)(1)(B).

In many cases, however, the vaccine recipient may have suffered an injury *not* of the type covered in the Vaccine Injury Table. In such instances, an alternative means exists to demonstrate entitlement to a Program award. That is, the petitioner may gain an award by showing that the vaccine recipient's injury was "caused-in-fact" by the vaccination in question. § 300aa-13(a)(1)(B); § 300aa-11(c)(1)(C)(ii). In such a situation, of course, the presumptions available under the Vaccine Injury Table are inoperative. The burden is on the petitioner to introduce evidence demonstrating that the vaccination actually caused the injury in question. *Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274, 1278 (Fed. Cir. 2005); *Hines v. Sec'y of Health & Human Servs.*, 940 F.2d 1518, 1525 (Fed. Cir. 1991).

The showing of "causation-in-fact" must satisfy the "preponderance of the evidence" standard, the same standard ordinarily used in tort litigation. § 300aa-13(a)(1)(A); *see also Althen*, 418 F.3d at 1279; *Hines*, 940 F.2d at 1525. Under that standard, the petitioner must show that it is "more probable than not" that the vaccination was the cause of the injury. *Althen*, 418 F.3d at 1279. The petitioner need not show that the vaccination was the sole cause of the injury or condition but must demonstrate that the vaccination was at least a "substantial factor" in causing the condition and was a "but for" cause. *Shyface v. Sec'y of Health & Human Servs.*, 165

F.3d 1344, 1352 (Fed. Cir. 1999). Thus, the petitioner must supply "proof of a logical sequence of cause and effect showing that the vaccination was the reason for the injury;" the logical sequence must be supported by "reputable medical or scientific explanation, *i.e*., evidence in the form of scientific studies or expert medical testimony." *Althen*, 418 F.3d at 1278; *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). A petitioner may not receive a Vaccine Program award based solely on his or her assertions; rather, the petition must be supported by either medical records or by the opinion of a competent physician. § 300aa-13(a)(1).

In what has become the predominant framing of this burden of proof, the *Althen* court described the "causation-in-fact" standard, as follows:

> Concisely stated, Althen's burden is to show by preponderant evidence that the vaccination brought about her injury by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of proximate temporal relationship between vaccination and injury. If Althen satisfies this burden, she is "entitled to recover unless the [government] shows, also by a preponderance of the evidence, that the injury was in fact caused by factors unrelated to the vaccine."

Althen, 418 F.3d at 1278 (citations omitted). The *Althen* court noted that a petitioner need not necessarily supply evidence from medical literature supporting petitioner's causation contention, so long as the petitioner supplies the medical opinion of an expert. *Id*. at 1279-80. The court also indicated that, in finding causation, a Program fact-finder may rely upon "circumstantial evidence," which the court found to be consistent with the "system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants." *Id*. at 1280.

Generally, respondent bears the burden of demonstrating the presence of any alternative cause by preponderant evidence only if petitioner satisfies her *prima facie* burden. § 300aa-13(a)(1)(B); *Walther v. Sec'y of Health & Human Servs*., 485 F.3d 1146, 1150 (Fed. Cir. 2007). However, respondent may also present evidence relating to an alternative cause to demonstrate the inadequacy of petitioner's evidence supporting her case in chief, but petitioner does not bear the burden of eliminating alternative causes where the other evidence on causation is sufficient to establish a *prima facie* case under *Althen*. *de Bazan v. Sec'y of Health & Human Servs*., 539 F.3d 1347, 1352-53 (Fed. Cir. 2008); *Walther*, 485 F.3d at 1150.

In this case, petitioner has alleged that her Tdap and/or polio vaccines caused or significantly aggravated ADEM, MS, or, more generally, CNS demyelination. Because these conditions are not listed on the Vaccine Injury Table relative to either the Tdap or polio vaccines, petitioner would need to satisfy the above-described *Althen* test for establishing causation-in-fact to prevail on the basis that her vaccinations initially caused her condition. At first, petitioner did focus on causation-in-fact based on the

Althen test, asserting her vaccine(s) caused an attack of acute partial transverse myelitis ("APTM"). (ECF No. 68.) However, respondent argued that petitioner suffered underlying, pre-existing MS that prevented her from demonstrating that her vaccinations initially caused her CNS demyelination. (ECF No. 70, p. 23.) This raises an additional question of whether petitioner experienced a significant aggravation of that condition consistent with her alternative pleading of the claim. (ECF No. 44, pp. 2-3.) In supplemental briefing on remand, petitioner clarifies that she contends that the attack of APTM she alleges to have been caused by her vaccines was a part of her MS disease process and constituted a significant aggravation of her MS. (ECF No. 97.)

The Vaccine Act defines a significant aggravation as any change for the worse in a pre-existing condition which results in markedly greater disability, pain, or illness accompanied by substantial deterioration of health. § 300aa-33(4). Where a petitioner in an off-Table case is seeking to prove that a vaccination aggravated a pre-existing injury, the petitioner must establish the three *Althen* prongs along with three additional factors described in the prior *Loving* case. *See Loving v. Sec'y of Health & Human Servs*., 86 Fed. Cl. 135, 144 (Fed. Cl. 2009) (combining the first three *Whitecotton* factors for claims regarding aggravation of a Table injury with the three *Althen* factors for off table injury claims to create a six-part test for off-Table aggravation claims); *see also W.C. v. Sec'y of Health & Human Servs*., 704 F.3d 1352, 1357 (Fed. Cir. 2013) (applying the six-part *Loving* test.). The additional *Loving* factors require petitioners to demonstrate aggravation by showing: (1) the vaccinee's condition prior to the administration of the vaccine, (2) the vaccinee's current condition, and (3) whether the vaccinee's current condition constitutes a "significant aggravation" of the condition prior to the vaccination. *Id*.

II. Procedural History

This case was originally assigned to Special Master Millman. (ECF No. 4.) Upon review of the records filed initially (Exs. 1-11), Special Master Millman raised the issue of a conflict in diagnosis. (ECF No. 9.) Special Master Millman suggested that the medical records favored the diagnosis of MS rather than ADEM. (*Id*. at 1.) Additionally, Special Master Millman noted that upon her review of the records, it appears that petitioner's onset of symptoms was June 4, 2016. (*Id*.)

Subsequently, petitioner filed additional records and a Statement of Completion. (ECF Nos. 14-16.) On April 24, 2018, respondent filed his Rule 4(c) report, recommending against compensation. (ECF No. 21.) Respondent indicated that the medical records presented an unclear diagnosis, and even assuming petitioner can establish that she suffered ADEM, petitioner failed to meet her burden in proving causation. (*Id*. at 16-17.)

On May 30, 2018, petitioner filed a letter from her treating physician, Dr. Slavenka Kam-Hansen to support her claim. (ECF No. 23; Ex. 17.) Dr. Kam-Hansen opined that petitioner suffered ADEM. (*Id*.) Respondent indicated that he intended to continue defending the claim. (ECF Nos. 24, 25.) However, petitioner advised that an

additional report from a different expert would be filed and, on May 24, 2019, petitioner filed a report from Dr. John G. Steel. (ECF No. 34; Ex. 20.) Dr. Steel did not support Dr. Kam-Hansen's ADEM opinion, opining instead that petitioner's correct diagnosis is MS.

This case was reassigned to my docket on June 6, 2019, upon Special Master Millman's retirement. (ECF No. 41.) Respondent requested that petitioner file an amended petition and updated medical records clarifying the nature of the injury in light of Dr. Steel's report opining that petitioner has MS rather than ADEM. (ECF No. 42.) On July 5, 2019, petitioner filed an amended petition alleging that her vaccinations caused her to suffer from "residual effects and complications of CNS demyelination, including but not limited to: fatigue, significantly heightened temperature sensitivity, pain and neuropathy in her right upper extremity, and the severe emotional and psychological effects of these and other chronic symptoms," noting that Dr. Steel felt the condition was best categorized as MS. (ECF No. 44, p. 2.)

In response, respondent filed a report from neurologist, Dr. Subramaniam Sriram. (ECF No. 52, Ex. A.) On January 31, 2020, petitioner filed Dr. Steel's supplemental expert report. (ECF No. 57, Ex. 54.) Thereafter, respondent filed his supplemental expert report from Dr. Sriram on May 14, 2020. (ECF No. 62, Ex. O.) Petitioner then requested that this case be resolved based on the written record. (ECF No. 63.)

On July 29, 2020, petitioner filed a motion for findings of facts and conclusions of law accompanied by a supporting memorandum. (ECF Nos. 67, 68.) In her motion, petitioner argued that the polio and Tdap vaccinations administered on April 4 and 22, 2016, triggered an attack of APTM that revealed her MS. (ECF No. 68.) Although petitioner acknowledged her expert had opined she had pre-existing subclinical MS and she had pleaded significant aggravation, significant aggravation was not raised in her motion for a ruling on the written record. (*Id*.) Instead, petitioner argued that she met the *Althen* test based on the post-vaccination APTM alone. (ECF No. 68.) On October 27, 2020, respondent filed a response contending that petitioner had not met her burden of proof and that the case should be dismissed. (ECF No. 70.) Respondent followed petitioner's framing of the case and also did not directly address the significant aggravation aspect of the pleading. (*Id*.) Petitioner filed a reply on December 4, 2020. (ECF No. 72.)

On February 1, 2021, I issued a ruling on entitlement finding petitioner entitled to compensation for a significant aggravation of pre-existing MS. (ECF No. 73; 2021 WL 750416.) Based on my review of the record as a whole, I concluded that the record did not preponderate in favor of a finding that petitioner suffered an injury of APTM separate from her MS, but nonetheless concluded that there was preponderant evidence that petitioner's post-vaccination demyelination constituted a vaccine-caused significant aggravation of her MS. (*Id*.) The parties subsequently resolved damages informally and I issued a decision awarding damages based on respondent's proffer on October 15, 2021. (ECF No. 84; 2021 WL 5055851.) Thereafter, respondent moved for review of the ruling on entitlement. (ECF No. 86.)

On April 1, 2022, the Court of Federal Claims issued an Opinion and Order granting respondent's motion, vacating the decision awarding damages, and remanding the case for further proceedings. (ECF No. 90; 159 Fed. Cl. 241.) Explaining that the parties had not had a full and fair opportunity to brief the issue of significant aggravation and assigning error to the ruling's treatment of a specific study by Langer-Gould, et al., the Court of Federal Claims concluded that the initial ruling on entitlement "adopted a theory of injury and causation that Petitioner never advanced and that does not appear to have been obvious from the evidence submitted." (ECF No. 90, p. 6.) The Court remanded the case "for the Special Master to consider the parties' arguments on aggravation of MS and to re-evaluate the medical evidence under the correct legal and scientific standards." (*Id*. at 10.) The Court also instructed that "[o]n remand, the Special Master should give the parties the opportunity for briefing – and, if appropriate, new written or live evidence – on whether Petitioner's vaccinations aggravated her MS." (*Id*. at 9-10.) The Court ordered that "[t]he special master shall issue a new entitlement decision within ninety days of this decision." (*Id.* at 10 (emphasis omitted).)

On April 15, 2022, a status conference was held to discuss the remand instructions. (ECF No. 94.) In discussing the Court of Federal Claims' Opinion and Order, the parties agreed to sequential briefing on the issue of significant aggravation in accordance with a mutually agreeable schedule. (*Id.*) The parties also decided to forgo supplementing the record with additional expert evidence.[3] (*Id*.) Petitioner filed her remand brief on May 10, 2022. (ECF No. 97.) Respondent filed his response on May 27, 2022. (ECF No. 98.) Petitioner's reply was filed June 3, 2022. (ECF No. 99.) Additionally, on June 16, 2022, the parties confirmed in a joint status report that in the event petitioner is found entitled to compensation on remand, damages should again be awarded based on the previously filed proffer at ECF No. 82. (ECF No. 101.)

III. Prefatory Explanation of Expert Reports and the Parties' Briefs Regarding Significant Aggravation

As noted in the procedural history above, three experts opined in this case, Drs. Kam-Hansen and Steel for petitioner and Dr. Sriram for respondent. Dr. Kam-Hansen discussed petitioner's condition as ADEM.[4] Drs. Steel and Sriram discussed petitioner's condition as MS, with Dr. Steel additionally asserting that TM has further relevance. Each expert's qualifications and opinion are summarized in the initial ruling on entitlement and no additional expert evidence was subsequently filed. Accordingly,

[3] In his supplemental brief, respondent confirms only that "[p]etitioner elected not to present any additional evidence." (ECF No. 98, p. 4, n. 2.) During the status conference, however, respondent's counsel additionally confirmed that respondent also did not wish to file additional evidence on remand so long as petitioner was not filing additional evidence. (*See* ECF No. 94 (confirming both parties agreed not to supplement the record with additional expert evidence).)

[4] The initial ruling on entitlement previously resolved the question of whether petitioner's diagnosis may have been ADEM as Dr. Kam-Hansen had opined, finding Dr. Kam-Hansen less persuasive and agreeing with Drs. Steel and Sriram that petitioner was properly diagnosed with MS. (ECF No. 73, p. 18.) Nothing in the subsequent history requires that analysis to be revisited. Accordingly, that finding with respect to diagnosis is incorporated by reference and the accompanying analysis is not repeated.

familiarity with the prior ruling is assumed and these summaries will not be repeated herein. However, due to the issues discussed by the Opinion and Order remanding this case and the parties' subsequent briefing regarding significant aggravation of petitioner's MS, additional discussion confirming the undersigned's understanding of Dr. Steel's opinion is warranted. In particular, respondent continues to contend on remand that Dr. Steel did not articulate a significant aggravation theory.

As observed by the reviewing Court, the phrasing of Dr. Steel's reports has led to some confusion that has been compounded by petitioner's initial approach to her own expert's reports. (ECF No. 90, p. 4.) Specifically, the Court observed that some of the language in Dr. Steel's report is consistent with a significant aggravation claim as the prior ruling on entitlement had initially concluded, but that "it is difficult to understand in the context of Dr. Steel's other opinions." (*Id*. at n. 3.) This confusion may be attributable in part to the fact that Dr. Steel did not specifically address the legal requirements of the Program. Often experts in this Program will provide a discussion addressing how their medical analysis relates to the relevant legal test (*e.g.,* discuss each *Althen* or *Loving* prong). Dr. Steel did not do this, leaving some room for subsequent interpretation. Additionally, three specific aspects of Dr. Steel's opinion, discussed below, potentially hinder the clarity of his reports: he refers to MS as a "red herring;" he characterizes petitioner's pre-existing MS merely as a "susceptibility" to a vaccine injury; and he references petitioner as having APTM. However, although some of this specific language seems as though it is in tension, Dr. Steel's medical opinion has been consistent in identifying a significant aggravation of petitioner's MS, notwithstanding his further references to transverse myelitis ("TM").

"Transverse myelitis is a common manifestation or presenting feature of acquired demyelinating diseases of the central nervous system." (Elliot M. Frohman & Dean M. Wingerchuk, *Transverse Myelitis,* 363 N. ENGL. J. MED. 564, 567 (2010) (Ex. 39).) Thus, when Dr. Steel wrote his first report in this case, he opined that:

> It is my opinion that [petitioner] experienced an attack of focal myelitis (inflammation of the spinal cord), caused by neuroimmune activation from receiving two vaccinations in close proximity. Focal myelitis can be associated with several different diagnoses, including Multiple Sclerosis . . . Following the attack of myelitis, [petitioner] meets current diagnostic criteria for Multiple Sclerosis. She experienced a clinically symptomatic event in a limited time window following vaccinations. This event, called a *Clinically Isolated Event*, was her first episode of neurological symptoms typical of an MS relapse in a person not known to have MS.

(Ex. 20, p. 3 (emphasis original).)

The literature filed in this case explains that "[a]ttack, relapse, exacerbation, and (when it is the first episode) clinically isolated syndrome are synonymous."[5] (Alan J.

[5] In her supplemental reply on remand, petitioner distinguishes her theory of a significant aggravation leading to clinically isolated syndrome as being distinct from a "relapse." (ECF No. 99, pp. 6-7.) Petitioner is correct insofar as clinically isolated syndrome refers uniquely to a first onset of neurologic symptoms.

Thompson, et al., *Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria,* 17 LANCET NEUROL. 162, 163 (2018) (Ex. C).) Dr. Steel explained that the spinal lesion at issue "is typical for an episode of focal spinal myelitis, as opposed to Transverse Myelitis (where the lesion would cross the spinal cord) or Neuromyelitis Optica. The lesion is radiographically typical for an MS plaque in the spinal cord." (Ex. 20, p. 3.) In his second report, Dr. Steel further refined his opinion to specify that the focal myelitis constituting petitioner's Clinically Isolated Syndrome ("CIS") is best characterized as APTM. (Ex. 54, pp. 3, 7.) However, he further indicated that "[a]cute partial myelitis is strongly associated with multiple sclerosis, either as an initial presenting disease or as part of the ongoing relapsing-remitting course of MS." (*Id*. at 3.)

Dr. Steel further explained that prior to vaccination petitioner's condition constituted what is called Radiographically Isolated Syndrome ("RIS"), which means MS was present, but evidenced only by lesions that could have been detected by MRI while the disease remained clinically silent by neurologic exam. (*Id*.) According to Dr. Steel, a person with RIS (or clinically silent MS) is already suffering autoimmune disease process even though their condition is subclinical. (Ex. 20, p. 5.) Thus, he clarified that in this case "[t]he vaccinations likely did not cause the MS but rather unmasked it, i.e. caused it to become clinically significant during her medical evaluation." (Ex. 20, p. 3.)

However, because he acknowledged that epidemiologic evidence specifically linking vaccination and MS relapse is lacking, Dr. Steel's initial report discussed the causes of immune-related demyelination in the broader context of other CNS demyelinating conditions, such as TM, based on the premise that petitioner's clinically isolated event (synonymous with a relapse or attack of MS) manifested as a focal myelitis of the spine. (Ex. 20, p. 4.) Dr. Steel characterized both MS and TM as existing within a category of immune-mediated CNS demyelinating disorders that differ epidemiologically but nonetheless have pathophysiologic commonalities. (*Id*. at 3-4.) He further asserted in his initial report that "there is epidemiological evidence and clinical experience that vaccinations, along with other non-specific immunogenic stresses, such as insect bites, minor trauma, surgery, infectious illness and environmental or psychological stress, may trigger an immune-mediated attack of demyelination *in persons who are susceptible* for genetic or other reasons." (Ex. 20, p. 4 (emphasis added).) By Dr. Steel's terms of reference, clinically silent MS is such a susceptibility due to the presence of ongoing autoimmunity. (Ex. 20, p. 5; Ex. 54, p. 7.)

More specifically, Dr. Steel suggested that MS tilts the CNS toward a pro-inflammatory state and that vaccines may further activate subclinical autoimmunity in the CNS as an unintended consequence of stimulating a heightened immune response. (Ex. 20, pp. 4-5.) In that regard he cited literature discussing a "fertile field" theory of autoimmunity specifically explaining why multiple immune stimuli may lead to clinically overt MS. (Ex 20, pp. 4-5 (citing Robert S. Fujinami et al., *Molecular Mimicry, Bystander Activation, or Viral Persistence: Infections and Autoimmune Disease,* 19(1) CLIN. MICROBIOL. REV. 80 (2006) (Ex. 24).) Thus, Dr. Steel stressed language from his supporting literature indicating that while TM may occur in isolation, "infection or immunization may also trigger attacks of myelitis in the context of underlying disease,

especially multiple sclerosis or neuromyelitis optica." (Ex. 20, pp. 4-5 (quoting Frohman & Wingerchuk, *supra,* at Ex. 39, p. 567).)

However, in responding to Dr. Steel's first report, Dr. Sriram focused on associational data specifically examining relapses in MS and dismissed any evidence regarding myelitis that was not strictly limited to the context of MS. (Ex. A, pp. 9-10.) Thus, when Dr. Steel wrote his second report responding to Dr. Sriram, he explained:

> [Petitioner] had clinically silent MS that came to light after her attack of TM but her MS is a red herring and has served to confuse the issue. In my report of 21 May 2019 I made no assertion of a causal relationship between the vaccines and MS. I gave a limited and carefully worded opinion regarding the myelitis only. Dr. Sriram's rebuttal of 22 November 2019 focused on MS but did not address the actual causal relationship that I have asserted, between [petitioner's] April 2016 vaccinations and her subsequent attack of spinal myelitis. By discussing MS *only*, he failed to address our central point.

(Ex. 54, p. 2 (emphasis added).)

Based at least in part on this passage, the parties originally briefed this case under the *Althen* test for causation-in-fact on the premise that petitioner suffered an acute TM injury that was distinct or separate from her more chronic course of MS. (ECF Nos. 68, 70, 72.) However, while some of Dr. Steel's language (such as the above "red herring" statement) may be viewed as lending support to this approach, it does not fully or accurately capture Dr. Steel's opinion. Dr. Steel was very clear in his first report in opining that petitioner's post-vaccination focal myelitis constituted CIS (*i.e.*, a first attack of MS) and continued to confirm in his second report that he understood the attack of myelitis to be a part of her ongoing MS, which was clinically silent prior to vaccination and became clinically overt after vaccination. (Ex. 54, pp. 3, 7.)

Additionally, Dr. Steel's causal theory was specifically premised on the presence of ongoing autoimmunity in the form of pre-existing subclinical MS, including citation to literature explaining why subclinical MS in particular may respond to a second immune insult. Dr. Steel opines that "[a]lthough there is little evidence that vaccinations cause multiple sclerosis in healthy patients, there is convincing evidence that vaccinations occasionally trigger single attacks of TM, ADEM, optic neuritis, and isolated spinal myelitis, and there is good reason to think that such an event is more likely in patients with subclinical MS." (Ex. 20, p. 5.) Ultimately, Dr. Steel concluded his final report by explaining that "Dr. Sriram's extensive discussion of the epidemiology of vaccinations and MS does not address my claim that the vaccine triggered an episode of spinal myelitis *in the context of the patient's pre-existing clinically silent MS*." (*Id*. at 7 (emphasis added)).

Importantly, notwithstanding how the parties initially postured the case in their briefs, respondent's expert, Dr. Sriram, fully understood Dr. Steel's opinion, albeit while strongly disagreeing. In response to Dr. Steel's first report, Dr. Sriram responded directly to Dr. Steel's line of reasoning. He offered the competing opinion that "[t]he prevailing opinion does not support the view that vaccines, even when given 'in close

temporal proximity,' in anyway way 'trigger' onset or relapses in patients with MS, including individuals with previously clinically silent MS." (Ex. A, p. 15.) In response to Dr. Steel's second report, Dr. Sriram correctly paraphrased Dr. Steel as opining that "what Dr. Steel is attempting to state is that while [petitioner] has MS *and myelitis is part of the MS syndrome*, her myelitis was caused by the vaccine." (Ex. O, p. 2 (emphasis added).) He countered that opinion by indicating that "Dr. Steel goes on to provide literature to support his position of a putative relationship between vaccines and transverse myelitis, fully aware that the literature does not provide any relationship, causal or otherwise, between transverse myelitis seen in patients with MS and receipt of vaccines." (Ex. O, p. 2.)

Dr. Sriram contended that "Dr. Steel's argument that 'very likely, the immune stimulation from multiple vaccinations altered her biological equilibrium,' resulting in an 'unmasking' of [petitioner's] MS, lacks any scientific foundation and contravenes what we know about MS as a disease process." (Ex. O, p. 6.) Thus, Dr. Sriram understood that Dr. Steel had offered an opinion that petitioner's vaccines had acted upon her MS disease process. However, because he opines that petitioner's MS is itself the sole explanation for petitioner's myelitis, Dr. Sriram characterized Dr. Steel's attempt to find causal factor for petitioner's disease-associated TM beyond the MS itself as "a mistake in clinical diagnosis." (Ex. O, p. 6.) Dr. Sriram contended that "[t]here is no confusion here about [petitioner's] MS diagnosis. The confusion is in trying to invoke an alternative etiology for transverse myelitis, when none is evident." (*Id*. at 2.)

Petitioner previously acknowledged in response to respondent's motion for review that in her initial motion for a ruling on the record she elided the significant aggravation opinion inherent to her expert's opinion. (ECF No. 89, p. 5 (expressing surprise the case was decided based on significant aggravation).) In supplemental briefing on remand, however, petitioner indicates that her original argument was made in light of the fact that Dr. Steel's reports "conceptualized her APTM as a discrete medical *event* caused by the vaccines." (ECF No. 97, p. 9 (emphasis added).) Petitioner now also confirms that the medical "event" in question – her alleged APTM – was, as Dr. Steel had opined, "radiographically typical for an MS plaque in the spinal cord." (*Id*. (quoting Ex. 20, p. 3).) Petitioner further contends that based on Dr. Steel's reports "[p]etitioner's attack of APTM can only be understood as the first clinical event in the progression of her MS which pre-existed her vaccinations." (*Id*.) Thus, petitioner argues that "her development of APTM secondary to vaccination did in fact constitute significant aggravation of her pre-existing MS per the *Loving* test." (*Id*. at 10.) Petitioner maintains that her prior discussion of the *Althen* test relative to APTM otherwise remains operative with respect to vaccine causation. After explaining that vaccine causation under *Loving* is decided under the same three prong test as *Althen*, petitioner incorporated by reference her prior argument as to why petitioner's APTM was caused by her vaccines. (*Id*. at 9-10 (citing ECF No. 68, pp. 15-25).)

In his supplemental brief on remand respondent likewise agrees that petitioner *did* suffer a significant aggravation of her MS within the legal framework of this Program. (ECF No. 98, p. 7, n. 3.) Respondent confirmed that for that reason he would not brief the first three *Loving* prongs on remand. (*Id*.) Rather, respondent contends that petitioner's claim should fail with respect to the fourth *Loving* / first *Althen* prong. (*Id*. at

6-7.) Respondent argues that Dr. Steel did not actually articulate a significant aggravation theory and that, even addressing such a theory *arguendo*, it is not reliably supported. (*Id*. at 7-13.) Because respondent asserts petitioner did not satisfy the fourth *Loving* prong regarding a theory of general causation, he concluded that petitioner therefore necessarily also could not satisfy *Loving* prongs five and six and opted not to provide any additional substantive argument regarding specific causation. (*Id*. at 13-14.)

However, like petitioner, respondent also incorporated by reference his arguments made in connection with petitioner's initial motion for a ruling on the written record. (ECF No. 70, p. 1, n. 1.) Although respondent has disputed that petitioner's expert articulated a theory of significant aggravation, respondent nonetheless responded to petitioner's initial motion with an *Althen* analysis that was responsive to such a theory, contending that "[p]etitioner has not demonstrated with preponderant evidence that the polio and Tdap vaccines can cause 'focal myelitis' or APTM in someone with MS, *i.e*., a relapse" and "[p]etitioner has also failed to prove by a preponderance of the evidence that, in this case, the vaccinations, rather than her underlying MS, caused her to experience a relapse." (ECF No. 70, p. 16.)

In light of all of the above, and having completed the remand instruction for additional briefing, I conclude that the parties have had a full and fair opportunity to develop the record of this case with regard to significant aggravation and that the case is ripe for resolution on the existing record.[6] I have considered the parties' additional arguments on remand and now reexamine petitioner's claim that her vaccinations significantly aggravated her pre-existing MS pursuant to the six-part *Loving* test and in light of the Court's guidance. Respondent's contention that Dr. Steel did not articulate a theory of significant aggravation of MS is not persuasive given the above.

Respondent relies heavily on the idea that Dr. Steel's reference to MS as a "susceptibility" necessarily indicates that his opinion was limited to an assertion that petitioner's pre-existing MS left her at heightened risk of TM *as a separate condition*. (ECF No. 98, pp. 7-8.) However, the term "susceptibility" is not in itself informative. A person can be said to be susceptible to a further harm just as a person can be said to be susceptible to a new harm. In this case, respondent's interpretation is incompatible with Dr. Steel's explicit assertion that petitioner's focal myelitis constituted CIS leading to a diagnosis of MS. While there is no doubt Dr. Steel finds acute TM and its causes to be relevant to his opinion, he specifically explained that TM does also occur as part of the MS disease process.

[6] As noted above, the parties have provided supplemental briefing on the question of significant aggravation, but otherwise confirmed during a status conference regarding the parameters of the remand that they did not wish to pursue further expert evidence. (ECF No. 94.) Special masters "must determine that the record is comprehensive and fully developed before ruling on the record." *Kreizenbeck v. Sec'y of Health & Human Servs.*, 945 F.3d 1362, 1366 (Fed. Cir. 2020) (citing *Simanski v. Sec'y of Health & Human Servs.*, 671 F.3d 1368, 1385 (Fed. Cir. 2012); *Jay v. Sec'y of Health & Human Servs.*, 998 F.2d 979, 983 (Fed. Cir. 1993.)); *see also* Vaccine Rule 8(d); Vaccine Rule 3(b)(2). The parties must have a full and fair opportunity to present their case and develop a record sufficient for review. *Id*.

Respondent also argues: "[p]etitioner further conceded that 'Dr. Steel's report and Petitioner's Memorandum conceptualized her APTM as a discrete medical event caused by the vaccines.' In other words, petitioner herself admits that Dr. Steel did not provide an opinion that her TM constituted a significant aggravation of her MS." (ECF No. 98, p. 8 (internal citation omitted).) Respondent's reinterpretation of petitioner's brief does not track. Petitioner specified in that same brief that "[p]etitioner's attack of APTM can only be understood as the first clinical event in the progression of her MS which pre-existed her vaccinations." (ECF No. 97, p. 9.) Moreover, a relapsing, remitting disease such as MS will necessarily comprise discrete events. Respondent's own expert, who clearly opines that MS is the only relevant condition, also characterizes the myelitis at issue in this case as a discrete medical event. He explains that in MS "[t]he first neurological event . . . is referred to as clinically isolated syndrome. In a patient later diagnosed with MS, the clinically isolated syndrome constitutes the first attack of the disease." (Ex. A, p. 7.) With regard to petitioner's own condition, he cites petitioner's MRIs to note that "[t]he enhancing lesions suggested a recent acute event." (Ex. O, p. 1.) Petitioner's reference to APTM as a "discrete medical event" is not contrary to a significant aggravation claim.

The remainder of the parties' arguments are addressed within the *Loving* analysis below.

IV. Medical History[7]

a. Pre-Vaccination

Petitioner, 67 at the time of the vaccinations at issue, has a history of Graves' disease. (Ex. 2, p. 51-54.) Petitioner sought treatment at Cambridge Health Alliance for her hypothyroid condition. (Ex. 3.) Her primary care records from 2010 to 2012 indicated she also had a bladder hernia, degenerative joint disease, and underwent a hysterectomy. (*Id*.) She is allergic to penicillin. (*Id*. at 7.) Petitioner has received several vaccinations in the past. (*Id*.) In 2011, petitioner received a physical exam in order to travel to Sri Lanka for work. (*Id*. at 28.) Her exam was normal and she requested several immunizations, denying any allergies to flu vaccine and history of Guillain-Barré syndrome. (*Id*. at 29-30, 33.) In 2015, petitioner had a physical therapy evaluation for ongoing knee and hip pain that worsened over 10 years. (Ex. 4, p. 141-43; Ex. 14, p. 44.)

b. Vaccination and Initial Treatment

Petitioner received a polio vaccination on April 4, 2016, and a Tdap vaccination more than two weeks after on April 22, 2016. (Ex. 1.) Petitioner had a mammogram and pap smear on April 4, 2016 (Ex. 5) and an evaluation for colonoscopy on April 8, 2016 (Ex. 7.) Petitioner had a colonoscopy on April 13, 2016. (Ex. 4, p. 116; Ex. 7, p. 6; Ex. 14, p. 28.) On April 21, 2016, petitioner visited Capital Cardiology Associate PA for an evaluation of an abnormal EKG. (Ex. 14, p. 24.) Dr. Bipinpreet Nagra

[7] This medical history is copied verbatim from the prior February 1, 2021, ruling on entitlement. No further medical records were filed subsequent to issuance of that ruling.

recommended an echocardiogram and stress test due to petitioner's family history. (*Id*.) On April 22, 2016, petitioner visited Lotus Medical Care for "PPD reading,[8] Tetanus shot, forms to be signed." (Ex. 19, p. 3.) Dr. Arkadiy Shraytman noted the visit was for screening of tuberculosis, follow up exam, and immunization. (*Id*. at 5.) Petitioner returned to Lotus Medical Center on May 27, 2016 for "Polio titer" and low back pain and primary generalized osteoarthritis were also noted as problems. (*Id*. at 7.) On June 1, 2016, petitioner visited Lotus Medical again to review her results and occipital neuralgia and iodine-deficiency were noted. (*Id*. at 10-12.)

On June 5, 2016, petitioner sought treatment at Capital Health Regional Medical Center emergency room for right side weakness and numbness, which began two nights prior. (Ex. 2, p. 50-51.) Two hours prior to arriving at the emergency room, petitioner reported experiencing itchiness and redness from scratching along AC joint and right shoulder. (Ex. 8, p. 39.) Petitioner had a consultation for a transient ischemic attack (TIA). (Ex. 8, p. 2.) Petitioner presented with achy pain in her right upper extremity, including her shoulder, neck stiffness, and mild weakness in her right grip. (*Id*.) Petitioner's head CT did not show any acute changes, only chronic lacunar infarctions. (*Id*.) Dr. Rajat Kumar examined petitioner and assessed that she presented with transient right upper extremity achiness and grip weakness. Dr. Kumar indicated that petitioner's CAT scan found lacunar infarcts and therefore, recommended additional imaging. (Ex. 2, pp. 60-61.) Petitioner underwent several imaging studies on June 5, 2016. Her angiography of the neck and head without contrast found no evidence of aneurysmal dilation or significant stenosis. (*Id*. at 36-37, 42-43.) Petitioner's brain MRI without contrast found no acute infarction, intracranial mass or hemorrhage, but did find multiple nonspecific foci of white matter hyperintensity that suggest a clinical diagnosis of a demyelinating disease. (*Id*. at 40.) Petitioner's head CT without contrast also found no signs for acute intracranial hemorrhage but revealed patchy regions of white matter hypoattenuation that may reflect microvascular ischemic changes, age indeterminate infarcts, and/or demyelinating disease. (*Id*. at 47-48.) Additionally, right maxillary sinus disease was noted. (*Id*. at 48.) Petitioner received steroids and her symptoms improved. (Ex. 8, p. 54.) Petitioner was discharged to rehab and was found to have an acute demyelinating disease with TM.[9] (Ex. 8, p. 33. 54.)

The next day, petitioner returned to Capital Health and was admitted. (Ex. 4, p. 43.) Petitioner also saw Dr. Kumar again for a neurology consult for weakness. Dr. Kumar noted white matter lesions in the periventricular region and subcortically that do not demonstrate enhancement but observed active demyelinating disease in the right lateral cervical area at C3-C4 that did enhance. (Ex. 8, p. 74.) Dr. Kumar assessed petitioner with acute demyelinating CNS disease, noting her presentation was "suggestive of multiple sclerosis." (Ex. 8, pp. 71-76.) Petitioner received a consultation

[8] PPD refers to a tuberculin skin test.

[9] In fact, the discharge diagnosis was "acute demyelinating CNS disease/multiple sclerosis." (Ex. 8, p. 54.) Only the "hospital course" notation references "acute demyelinating disease with transverse myelitis." (*Id.*)

from Dr. Michael S. Beede on June 11, 2016, for "positive ANA, in the context of previous Graves' disease, and with new multiple sclerosis." (Ex. 8, p. 64.) Petitioner's brain and cervical MRI were compatible with the diagnosis of MS. (*Id*. at 64, 152.) Dr. Beede indicated that the positive ANA may be either from petitioner's thyroid disease or MS. (*Id*. at 65.)

Petitioner underwent various MR imaging on June 6, 2016. (Ex. 2, pp. 16-28.) An MRI of the thoracic spine with and without contrast revealed overall no abnormal signal or enhancement within the thoracic spinal cord. (*Id*. at 16.) However, certain regions demonstrated enhancement that were indeterminate and there were mild degenerative changes in the thoracic spine. (*Id*. at 16-17.) Additionally, there was a small disc protrusion that caused mild right subarticular zone stenosis. Follow up was recommended. (*Id*. at 17.) The MRI of the lumbar spine with and without contrast showed degenerative changes in the lumbar spine and a possible impingement upon certain nerve roots. Additionally, the MRI findings also suggested an atypical hemangioma and follow up was recommended. (*Id*. at 20-21.) The MRI of the cervical spine with and without contrast found an abnormal signal within the spinal cord involving the right lateral column. (*Id*. at 23-24.) The brain MRI with and without contrast taken on June 6, 2016, was compared with the MRI without contrast taken on the day before. The more recent MRI still showed multiple regions of white matter hyperintensity mostly in the periventricular and subcortical area running perpendicular to the ependymal surface regions; however, the white matter lesions did not demonstrate enhancement. (Ex. 2, pp. 27-28.) She had a chest x-ray that showed bibasilar subsegmental atelectasis and cardiomegaly. (*Id*. at 31.) And petitioner's head CT did not reveal any acute intracranial findings. However, "scattered areas of white matter hypoattenuation are unchanged with corresponding signal abnormality on the preceding brain MRI, most compatible with a demyelinating process. There is no mass effect." (*Id*. at 34.)

Petitioner was discharged to rehab from Capital Health on June 14, 2016, with multiple diagnoses including acute demyelinating CNS disease / MS, acute weakness of the right side. (*Id*. at 50.) During her stay, petitioner was found to have an acute demyelinating disease with TM and was treated with high dosage of steroids. Petitioner showed drastic improvements but was still weak and therefore needs rehab and a neurological follow up. (*Id*. at 51.)

Petitioner was admitted into St. Lawrence Rehabilitation Center for general debility upon discharge from Capital Health. (Ex. 4, p. 10.) Dr. Madhu Jain, upon review of systems, noted that petitioner reported double vision in the right eye (premorbid). (*Id*.) Upon examination, petitioner was noted with decreased grip strength and overall strength, decreased fine motor control, and decreased balance. Dr. Jain's impression was mild right-side weakness with new onset diagnosis of MS post steroid therapy with continued weakness in right upper and lower extremity. Petitioner was recommended both physical and occupational therapy to address transfers, ambulation, and self-care. (*Id*. at 11.)

On June 23, 2016, petitioner visited Dr. Shukia for a follow up evaluation of her right-sided weakness. (Ex. 2, p. 2.) Petitioner reported that while she was at Capital Health System, she had a brain MRI that showed some white matter changes, but a couple of days after being discharged, she experienced right leg weakness and returned for a C-spine MRI, which showed an enhancing area of abnormal signal. (*Id*. at 3.) Petitioner sought treatment at St. Lawrence Rehab and reported that her strength significantly improved. Dr. Shukia reported that other than a mild limping feeling in the right leg, petitioner seemed to have returned to baseline. Dr. Shukia suggested a full work up including a spinal tap. However, he noted that petitioner did not have any episode of blindness and that "this lesion in the C-spine is also not more than 2 segments of the cervical column." Petitioner also visited Dr. Shukia on July 14, 2016, for a follow up evaluation for history of possibility of demyelinating disease. (Ex. 2, p. 1.) Dr. Shukia noted that petitioner had a "somewhat bloody" spinal tap that tested positive for oligoclonal bands. (*Id*.) Upon physical examination, petitioner presented normal upper and lower extremity strength. Dr. Shukia's impression was that petitioner presented with a demyelinating disease, most likely MS and discussed petitioner's options regarding treatment and medicine during this visit. (*Id*.)

Petitioner had an occupational therapy evaluation and treatment on June 27, 2016, for MS exacerbation. (Ex. 4, p. 43.) Petitioner showed improvements after one month in rehabilitation in upper extremity strength, coordination, and endurance, but had mild deficits in right shoulder strength and fine motor coordination. (Ex. 4, p. 46.)

c. Subsequent Post-Vaccination History

On July 6, 2016, petitioner received an initial consultation from Dr. Chitharanjan Rao at the Lawrenceville Neurology Center. (Ex. 4, p. 8.) Dr. Rao's assessment was that petitioner has a history of acute/subacute onset right sided weakness since June 5, 2016 "in the setting of TDP vaccination in early April 2016." (*Id*.) However, the symptoms have nearly resolved and no further episodes, and therefore petitioner is normal from a neurological standpoint notwithstanding the mild sensory loss in her left hand and diffuse hyperreflexia. Dr. Rao diagnosed petitioner with likely ADEM, probably related to her vaccination, but MS is a possibility. (*Id*.) Dr. Rao recommended continuing physical and occupational therapy and avoiding receiving vaccinations for the season. (*Id*. at 9.)

Petitioner returned to Lotus Medical on July 12, 2016, for a follow up appointment post hospitalization for possible MS. (Ex. 19, p. 12.) Dr. Shraytman ruled out ADEM but noted MS and low back pain among petitioner's list of problems. (*Id*. at 13-14.)

Aside from seeking treatment from Dr. Rao, petitioner continued visiting Dr. Shukia for her demyelinating disease. (Ex. 4, p. 104; Ex. 14, p. 18.) Dr. Shukia continued to believe that petitioner most likely has MS. (*Id*.) Petitioner had a broken pinky toe and was treated at Champion Orthopedics on August 1, 2016. (Ex. 4, pp. 95-97.) Petitioner underwent physical therapy at St. Lawrence Rehabilitation Center from June 27, 2016 and was discharged on August 10, 2016. (Ex. 6.) Petitioner "progressed

very well with therapy [and met] all goals therefore has been discharged with [home exercise program]." (*Id.* at 5.)

A cervical spine MRI performed on August 17, 2016, again showed lesions and enhancement compatible with a demyelinating process related to petitioner's history of MS. (Ex. 4, p. 49-51.) Petitioner received a follow up evaluation for her MS from Dr. Rao on August 19, 2016.[10] (Ex. 4, p. 1; Ex. 14, p. 1.) According to Dr. Rao, petitioner's VEP tests indicated a mild conduction delay involving the right optic nerve but her spinal tap was traumatic and negative for oligoclonal bands.[11] (Ex. 4, p. 1, 33-35, 52.) Petitioner reported paresthesia in her right and left upper extremity, numbness in her left hand, hyperpathia to touch, but believed she was much better with nearly normal gait. (*Id*. at 1.) Upon review of petitioner's MRI imaging, Dr. Rao indicated that the results were consistent with a history of MS and that no new abnormal findings were detected. (*Id*. at 2.)

Petitioner began receiving primary care at Beth Israel Deaconess Medical Center after moving back to Boston from New Jersey in September 2016. (Ex. 11, p. 2.) Petitioner reported that three neurologists had diagnosed her with MS; however, she "saw a neurologist in whom she now has a lot of confidence who diagnosed her as having [ADEM]." (*Id*.) Petitioner reported experiencing continuing weakness and dysesthesias and acute cramping in right upper extremity. (*Id*.) Dr. Harvey Bidwell noted ADEM after polio vaccine and Tdap injection as part of petitioner's history of present illness. (*Id*. at 12.) Dr. Bidwell accepted petitioner's diagnosis of ADEM and referred petitioner for physical and occupational therapy. (*Id*. at 25.) In addition, petitioner saw Simone D. Martell, LCSW, for emotional support in coping with a neurological disease diagnosis. (*Id*. at 10-12, 17-21.)

On September 20, 2016, petitioner was admitted to the emergency department at Beth Israel Deaconess Medical Central for seizures. (Ex. 10, p. 3.) Petitioner reported a recent diagnosis of ADEM[12] and symptoms of aura and weakness to extremities (right[13] leg arm and leg numbness). (*Id*. at 6, 8.) Petitioner had a neurology consult for right hand and leg spasms. (*Id*. at 27.) Upon examination Dr. Fay Gao found that petitioner had subjective positive sensory symptoms but no objective deficits to all sensory modalities tested. (*Id*. at 30.) Dr. Gao noted that "[w]hile tonic spasm can occur in the setting of recent demyelination, [petitioner] does not have any other

[10] Petitioner additionally had follow-up visits with Dr. Rao on July 28, 2016, August 18, 2016. The exams were similar and Dr. Rao had the same observations/conclusions.

[11] As Special Master Millman previously observed, Dr. Rao incorrectly stated that petitioner did not have oligoclonal bands and seemed unaware that petitioner had abnormal VEP on the right. (ECF No. 9, p. 1.) Dr. Rao concluded that the lesions of her spinal cord were consistent with petitioner's history of MS, yet Dr. Rao concluded that petitioner did not have MS but ADEM. (*Id*.)

[12] Petitioner reported a possible diagnosis of ADEM or MS. (Ex. 10, p. 22.)

[13] In another part of the emergency room records, it was noted that petitioner had left lower extremity numbness. (Ex. 10, p. 11.)

significant signs of myelopathy such as weakness, loss of sensation, though her reflexes are somewhat brisk. A superimposed peripheral sensory neuropathy is possible as well." (*Id*. at 30-31.) In addition, since the symptoms were brief and resolved, Dr. Gao noted that petitioner should follow up with her neurologist and thus, no additional head imaging was ordered; however, Dr. Gao recommended blood work up and routine EEG. (*Id*. at 13, 31.) Petitioner was discharged on the same day. (*Id*. at 20, 26.)

On September 27, 2016, petitioner had a neurological consultation with Dr. Slavenka Kam-Hansen for complaints of development of left lower leg burning following vaccinations. (Ex. 15, p. 5.) Toward the end of October in 2016, petitioner returned to the Japanese Acupuncture Center of Independent Practitioners for acupuncture treatment. (Ex. 9, p. 2.) Petitioner experienced "hot spots" in legs, fatigue, and symptoms in her right and left arm. (*Id*. at 3-6.) Petitioner continued seeking weekly treatment throughout 2016 and into January 2017 but remained symptomatic. (*Id*. at 6-7.)

Petitioner returned to Dr. Kam-Hansen seven weeks after her initial consultation on November 14, 2016. (Ex. 15, p. 15.) Dr. Kam-Hansen listed petitioner's neurological problems as presumed ADEM following two vaccinations in April, where the onset of lower leg burning sensation and pressure in right shoulder began in May. (*Id*.) Dr. Kam-Hansen noted that petitioner was initially diagnosed with MS until Dr. Rao diagnosed ADEM instead. Petitioner reported continued burning sensation in her left shin, foot, and hip as well as throbbing, achy, and pins and needles sensation in her right shoulder running down to her fingertips. (*Id*.) Additionally, petitioner reported experiencing focal seizures again. (*Id*.) Dr. Kam-Hansen concluded that petitioner has ADEM rather than MS, but time will give a clearer diagnosis since recovery after ADEM can take months. (*Id*. at 16.) Subsequent imaging was ordered and petitioner returned to see Dr. Kam-Hansen to discuss the results. (*Id*. at 18.) Petitioner's imaging did not show any new lesions and the cervical cord lesion decreased. (*Id*. at 18, 51-54)

On March 23, 2017, petitioner received another physical therapy evaluation for her diffuse body aches, balance issues, and weakness. (Ex. 15, p. 21.) Petitioner reported sensitivity to cold in her right arm and hot spots and weakness in her legs. (*Id*.) The evaluation resulted in physical therapy diagnoses including impaired muscle performance and "impaired motor function and sensory integrity associated with non-progressive disorders of the CNS acquired in adolescent or adulthood." (*Id*.) It was noted that petitioner's presentation seems to be a combination of ADEM related impairments combined with deconditioning; however, petitioner had a good prognosis in light of high functionality and general improvement since onset of symptoms. (*Id*. at 25-26.) She continued with therapy.

On August 3, 2017, petitioner visited Dr. Bidwell for a follow up visit. Petitioner reported fatigue, incontinence, and remaining symptoms of burning sensation in her left shin and foot, throbbing, achy, and pins and needle sensation in her right shoulder to her fingertips. (Ex. 50, p. 4.) Dr. Bidwell assessed that petitioner has a history of ADEM following vaccination in April 2016 and still has fatigue, sensory and pain

symptoms, and incontinence. (*Id*. at 6.) He added that petitioner's November 2016 imaging did not show any new lesions and the lesions in her spinal cord decreased. (*Id*.) Additionally, petitioner saw Dr. Bidwell for urinary and fecal incontinence worsened by petitioner's ADEM in August 17, 2017. (Ex. 15, p. 48; Ex. 50, p. 8-9.) Thereafter, petitioner had a urogynecology evaluation at Beth Israel Deaconess Medical Center in October 2017. (Ex. 16, p. 9; Ex. 50, p. 12.) Petitioner was diagnosed with Stage II cystocele and urogenital atrophy. (Ex. 50, p. 16.) Dr. Roger Lefevre indicated that "[a]lthough her documented ADEM lesions occur in the C3-C4 distribution, her urinary and fecal incontinence may be due in part to autonomic/neurogenic dysfunction in the setting of ADEM." (Ex. 16, p. 13.)

Petitioner visited the emergency department in late October 2017 due to swelling, pain, and tenderness in her right toes, which was caused by stubbing them against a chair. (Ex. 51, p. 37.) Petitioner had a closed displaced fracture, but otherwise stable and released home. (*Id*. at 39.) Additionally, on November 15, 2017, petitioner presented to Dr. Adam Landsman as a new patient with complaint of pain in her right foot. (*Id*. at 41.) Dr. Landsman did not recommend surgery, but instead for follow up evaluations and repeat radiographs. (*Id*. at 42.) Thereafter, also in November 2017, petitioner returned to Dr. Bidwell reporting that she had a fracture in her toe. (Ex. 50, p. 25.) Otherwise, this visit was similar to petitioner's visit in August with no particular changes to petitioner's neurological symptoms. (*Id*. at 25-28.)

In early 2018, petitioner sought treatment again from Dr. David Baron, whom she last saw in 2012. (Ex. 51, p. 43.) Petitioner reported developing ADEM following polio and Tdap vaccinations and experiencing mild spasms in her left arm. (*Id*.) On March 22, 2018, petitioner went to the emergency department following a mechanical fall and complained of left wrist pain. (*Id*. at 46.) She was diagnosed with a closed nondisplaced fracture in her left hand. (*Id*. at 49.)

During an encounter on August 13, 2018, with Dr. Baron, petitioner reported that her right arm numbness/encephalopathy "has not been as bad recently." (Ex. 51, p. 57.) Dr. Baron accepted ADEM as the primary encounter diagnosis and noted that it was "thought due to vaccine." (*Id*. at 58.) Two months later, during another encounter, petitioner was minimally symptomatic and stopped taking gabapentin. (*Id*. at 61.) At this visit in October 2018, Dr. Baron assessed petitioner with neuropathic pain generally as the primary encounter diagnosis. (*Id*.)

In March 2019, petitioner returned to Dr. Bidwell for a referral for physical therapy to improve balance and leg strength. (Ex. 50, p. 30.) Additionally, petitioner requested a form to that would allow her to avoid vaccinations. (*Id*.) Aside from Dr. Bidwell, petitioner also sought care at Cambridge Health Alliance. During a visit on March 27, 2019, petitioner indicated that she hasn't had symptoms for the past two years but started having right arm paresthesia and right shoulder pain over the past few days. (Ex. 51, p. 2; Ex. 53, p. 2.) After consulting with the on-call neurologist and Dr. Kam-Hansen, Dr. Jaeyoung Yang reported that petitioner's neurological exam was normal. (Ex. 51, p. 67.)

In April 2019, petitioner continued seeking urology treatment from Dr. Heidi Rayala. (Ex. 51, p. 7.) Dr. Rayala described petitioner as having a history of ADEM following vaccination in 2016, "which is when her urination problems started." (*Id*.) In October 2019, petitioner visited Cambridge Health Alliance to visit Dr. Baron, her PCP. (Ex. 53, p. 2.) Dr. Baron noted that petitioner was doing well and the plan was to follow up with Dr. Kam-Hansen regarding her neurological symptoms. (*Id*. at 9.)

V. Analysis Regarding Petitioner's Multiple Sclerosis

For the reasons discussed above, the relevant framework for determining whether petitioner's injury was caused-in-fact by her vaccination(s) is the six-part *Loving* test for significant aggravation claims. *Loving* prongs one through three are addressed first. These prongs examine petitioner's condition before and after vaccination, ultimately asking whether petitioner suffered a worsening of her pre-existing condition subsequent to vaccination. Finding that petitioner did experience a worsening of her pre-existing MS, the analysis turns to whether that significant aggravation was caused by her vaccine(s).

The remaining three *Loving* prongs match the three-part *Althen* test for determining causation-in-fact. For the reasons discussed below, I find that petitioner has preponderantly established all three of these prongs. The fourth *Loving* prong speaks to general causation, addressing whether petitioner has presented a medical theory establishing that her vaccines can cause her alleged injury. This is the most extensively discussed point of analysis below. *Loving* prongs five and six address specific causation, asking whether there is a logical sequence of cause and effect to establish vaccine causation in this specific instance (*Loving* prong five) and whether the timing of the injury is medically appropriate to infer vaccine causation (*Loving* prong six). These two prongs are discussed together, starting out of typical order with *Loving* prong six. Lastly, respondent's potential demonstration of a causal factor unrelated to vaccination is briefly addressed.

a. *Loving* Prongs One Through Three

i. *Loving* prong one

Petitioner's pre-vaccination medical records contain no significant evidence of any outward clinical signs or symptoms of MS or any other CNS demyelinating condition prior to her vaccination. However, both Dr. Steel and Dr. Sriram agree that petitioner's post-vaccination MRI study of June 5, 2016, revealed non-enhancing lesions that suggest she had pre-existing, subclinical MS prior to her vaccination. (Ex. 20, pp. 3-4; Ex. A, pp. 7-8.) Specifically, Dr. Steel characterized petitioner's MRI as revealing "lesions in the brain consistent with MS, likely preexistent, likely old, and clinically silent" and opined that this pre-existing MS represented an underlying susceptibility. (Ex. 54, p. 6.) He explained that petitioner's pre-vaccination status constituted RIS, which means petitioner had lesions visible to MRI, but no clinical neurologic symptoms. (Ex. 20, p. 3.)

Thus, petitioner argues in her supplemental brief that "[i]n sum, the parties' experts agree that [petitioner's] June 5, 2016, brain MRI provides objective evidence that she was already undergoing a clinically silent MS disease process prior to her April 2016 vaccinations." (ECF No. 97, p. 11.) Respondent opted not to provide supplemental briefing with respect to *Loving* prong one. (ECF No. 98, p. 7, n. 3.)

The weight of evidence preponderantly establishes that petitioner had pre-existing clinically silent MS prior to the receipt of her polio and Tdap vaccinations in April 2016.

ii. *Loving* prong two

It is undisputed that petitioner experienced an attack of CNS demyelination by early June of 2016. (Ex. 2, p. 51.) This is evidenced both by petitioner's first outward clinical manifestation of symptoms and also by objective imaging. (*Id*.) Petitioner first sought treatment on June 5, 2016, for right side weakness and numbness, which began two nights prior, *i.e*., June 3, 2016. (*Id.* at 51, 59.) On June 6, 2016, a subsequent MRI showed white matter lesions in the periventricular region and subcortically that do not demonstrate enhancement, but also active demyelinating disease in the right lateral cervical area at C3-C4 that did enhance. (Ex. 8, p. 74.) Both parties present experts (Drs. Steel and Sriram) who agree that ultimately MS is petitioner's correct diagnosis following this attack. (Ex. 20, p. 3; Ex. A, p. 7.) It is also undisputed that petitioner was ultimately diagnosed with MS (correctly according to Drs. Steel and Sriram) by at least some of her physicians following this initial attack of CNS demyelination. (Ex. 2, pp. 2, 50; Ex. 14, p. 18; Ex. 20, p. 3; Ex. 54, p. 3; Ex. A, p. 8; Ex. O, p. 6; ECF No. 70, p. 12.)

More specifically, Dr. Steel has opined that this post-vaccination presentation constituted an attack of focal myelitis of the spine. He also explained that "[s]he experienced a clinically symptomatic event in a limited time window following vaccinations. This event, called a Clinically Isolated Event, was her first episode of neurological symptoms typical of an MS relapse in a person not known to have MS." (Ex. 20, p. 3.) Dr. Sriram likewise agrees that when petitioner sought treatment on June 5, 2016, she had an enhancing spinal lesion evidenced on MRI and that this spinal cord demyelination led to her symptoms of arm and leg weakness. (Ex. A, pp. 8-9.) He further agreed that this was petitioner's first clinical attack of her MS. (*Id*. at 8.)

In her supplemental brief, petitioner contends that "[t]here is no dispute that she experienced a clinically acute episode of CNS demyelination following her vaccinations." (ECF No. 97, p. 12.) Respondent opted not to provide supplemental briefing with respect to *Loving* prong two. (ECF No. 98, p. 7, n. 3.)

The weight of evidence preponderantly establishes that petitioner suffered spinal myelitis constituting her first clinical attack of her pre-existing MS by no later than June 3, 2016. To the extent Dr. Steel additionally characterized petitioner's spinal myelitis as APTM (Ex. 54, p. 7), this is addressed under *Loving* prong three.

iii. *Loving* prong three

There has been some suggestion, most notably from petitioner herself in her original motion for a ruling on the record, that the post-vaccination myelitis forming the

basis for this claim should be considered as APTM separately from petitioner's MS. For his part, Dr. Steel indicated that petitioner suffered an attack of APTM, but also stressed that APTM is associated with MS and that petitioner's focal myelitis constituted CIS. (Ex. 20, p. 3; Ex. 54, pp. 3, 7.) Petitioner now acknowledges in her supplemental brief that her APTM was a part of her MS, though she still maintains that the APTM nonetheless constituted a discrete medical "event." (ECF No. 97, p. 9.) The record preponderates in favor of a finding that petitioner's APTM is a manifestation of her pre-existing MS.

Petitioner has filed literature broadly cautioning that idiopathic or primary TM should be distinguished from disease-associated TM, suggesting that "[i]dentification of etiologies may suggest medical treatment, whereas no clearly established medical treatment currently exists for idiopathic ATM." (Transverse Myelitis Consortium Working Group, *Proposed Diagnostic Criteria and Nosology of Acute Transverse Myelitis*, 59 NEUROLOGY 499, 499 (2002) (Ex. 68).) Moreover, Dr. Sriram stressed that MS is an exclusionary factor in the diagnosis of TM under the prevailing diagnostic criteria. (Ex. O, pp. 2-3.) Dr. Steel further suggested that subsequent literature distinguishes between idiopathic TM, APTM, and acute complete TM ("ACTM"). (Thomas F. Scott, *Nosology of Idiopathic Transverse Myelitis Syndromes*, 115 ACTA NEUROL. SCAND. 371, 373 (2007) (Ex. 65) (Table 1)).) Dr. Steel contends that petitioner's case is consistent with the latter APTM. (*Id.*)

Critically, however, Dr. Steel acknowledges that APTM, in contrast to ACTM, "is strongly associated with multiple sclerosis, either as an initial presenting disease or as part of the ongoing relapsing-remitting course of MS." (*Id.*) Dr. Scott explains that, while not all cases of APTM will ultimately constitute clinically definite MS ("CDMS"), "[w]hen patients present with APTM and cerebral MRI showing lesions typical of MS, the transition rate to CDMS is known to be quite high, in the range of 80-90% within a few years." (Scott, *supra,* at Ex. 65, p. 375.) While patients with MS often initially present with APTM, it is not accurate to say that patients with MS also carry *a diagnosis* of APTM. Rather, as Dr. Sriram explains, once the MS diagnosis is made, the prior TM "becomes a feature" of the MS. (Ex. O, p. 3.)

The literature that Dr. Steel cited for the specific proposition that immunization may trigger attacks of myelitis in the context of underlying disease (Frohman and Wingerchuk), also specifically indicates partial TM is associated with a high risk of MS. (Frohman & Wingerchuk, *supra,* at Ex. 39, p. 566 (chart)).) That literature includes a diagnostic flow chart that indicates that findings of demyelination on brain MRI, oligoclonal bands, and an abnormal visual evoked response should lead to the conclusion of a high risk of MS rather than a diagnosis of TM. (*Id.*) Under this framework, only the absence of all of these findings would allow for a reconsideration of the clinical history that could potentially lead to a diagnosis of idiopathic, postinfectious, or post-vaccination TM. (*Id.*) Thus, respondent argued that "if Dr. Steel had employed the methodology outlined by Frohman and Wingerchuk, he would have concluded that

petitioner's 'focal myelitis' or APTM was caused by her underlying MS, not her preceding vaccinations."[14] (ECF No. 70, p. 23.)

In that regard, Dr. Steel also acknowledged that petitioner's overall presentation around the time her symptoms first manifested is more consistent with MS than with an isolated attack of TM. (Ex. 20, p. 3.) Dr. Steel opined that petitioner's spinal lesion is distinct from complete TM, because it did not cross the midline of the spinal cord. (*Id*.) He also opined that the presence of oligoclonal bands and optic neuropathy distinguish petitioner's condition from TM generally. (*Id*.) Further, there is agreement that petitioner's presentation at the time of her clinical attack evidenced dissemination in time and space, a key diagnostic consideration for MS that is not consistent with an isolated attack. (Ex. 20, p. 3; Ex. A, pp. 7-8; *see also* Thompson et al., *supra*, at Ex. C.) Dr. Steel explained that petitioner's spinal lesion, though typical of MS, is not itself diagnostic. (Ex. 20, p. 3.) However, he agreed that the presence of oligoclonal bands in petitioner's cerebral spinal fluid suggested dissemination in time. (*Id*.) Dr. Steel further indicated that petitioner's abnormal visual evoked responses in the right optic nerve evidenced dissemination in space. (*Id*.) Additionally, although he stressed that petitioner's outward clinical symptoms began post-vaccination, her MRI "revealed lesions in the brain consistent with MS, likely preexistent, likely old, and clinically silent." (Ex. 54, p. 6.) These factors support the understanding that petitioner's APTM would be considered a part of her MS by Frohman & Wingerchuk.

However, although Frohman and Wingerchuk diagnostically distinguish between post-vaccination TM and disease-associated TM, Dr. Steel also quotes language that demonstrates the authors believe disease-associated TM can still be vaccine triggered. Specifically, Dr. Steel notes that the authors state: "[t]he occurrence of transverse myelitis after infection or vaccination does not preclude the need for further evaluation, since infection or immunization may also trigger attacks of myelitis in the context of underlying disease (especially multiple sclerosis or neuromyelitis optica)." (Frohman & Wingerchuk, *supra,* at Ex. 39, p. 567.) This language underscores Dr. Steel's premise that vaccine-related TM is possible "in the context of the patient's pre-existing clinically silent MS." (Ex. 54, p. 7.)

Based on this statement, Dr. Sriram contends that Frohman and Wingerchuk take inherently contradictory positions. (Ex. O, pp. 4-5.) He states that the quoted language is incompatible with a further discussion by the authors distinguishing post-vaccination TM from TM in patients with MS. Specifically, he quotes the following language:

> identifying the cause of transverse myelitis facilitates the prediction of the future clinical course and informs the decision about whether to provide prophylaxis against future neurologic events. The postinfectious, postvaccination, and idiopathic forms of transverse myelitis are usually

[14] Respondent is correct that Frohman and Wingerchuk's diagnostic method would lead to a diagnosis of MS rather than post-vaccination APTM; however, as discussed further below, respondent misstates the Frohman and Wingerchuk article to the extent he presents the authors as opining that the MS diagnosis is mutually exclusive of vaccine causation.

> monophasic syndromes, whereas multiple sclerosis and neuromyelitis optica – spectrum disorders are relapsing diseases that are associated with high risk of future attacks of transverse myelitis and other neurologic events.

(Ex. O, p. 5 (quoting Frohman & Wingerchuk, *supra,* at Ex. 39, p. 567).)

Dr. Sriram opines that "Frohman and Wingerchuk cannot simultaneously claim that vaccines cause transverse myelitis in patients with underlying MS and at the same time draw a line between postvaccination transverse myelitis and MS-associated transverse myelitis." (Ex. O, p. 5.) However, the contradiction Dr. Sriram posits only exists if one assumes the authors share Dr. Sriram's overall point of view regarding clinical parsimony rather than agreeing with Dr. Steel's opinion that MS is multifactorial and that neurologic events in MS respond to external triggers, including vaccines.[15] This difference of opinion is explored further with respect to *Loving* prong four, below.

For purposes of *Loving* prong three, however, petitioner's supplemental brief cites approvingly to respondent's expert's statement that "TM becomes a feature of MS once the MS diagnosis is made[.]" (ECF No. 97, p. 13 (quoting Ex. O, p. 3).) Thus, petitioner contends that "both experts are clear that petitioner is best thought of as having experienced an attack of spinal myelitis as the first clinical manifestation of her MS, and as part of the progress of the disease." (ECF No. 97, p. 12.) Because Dr. Steel opined that petitioner's condition went from "clinically silent" to "clinically significant," petitioner contends that "[i]f a patient's underlying disease process goes from clinical silence to extreme clinical salience, it is inarguable that that patient's condition has undergone a 'significant aggravation.'" (*Id.* at 12-13.) Respondent opted not to provide supplemental briefing with respect to *Loving* prong three, agreeing that petitioner did suffer a significant aggravation of her MS. (ECF No. 98, p. 7, n. 3.)

In light of the above, the evidence preponderates in favor of a finding that diagnostically speaking petitioner's post-vaccination demyelination is better understood as a part of the course of her pre-existing MS rather than as a separate idiopathic APTM. Additionally, combined with the findings pursuant to *Loving* prongs one and two, there is preponderant evidence on this record that due to this attack of myelitis petitioner suffered a change for the worse in her pre-existing MS, resulting in markedly greater disability, pain, or illness accompanied by substantial deterioration of health. § 300aa-33(4). As explained above, Dr. Steel opines that petitioner suffered RIS pre-vaccination and experienced a post-vaccination "unmasking" of her MS in the form of a spinal myelitis constituting CIS. Although Dr. Sriram ultimately disputes vaccine-causation, he likewise agrees that the spinal myelitis at issue was a part of the course of

[15] Per the diagnostic flow chart created by Frohman and Wingerchuk, only if the patient is at "low risk" for MS is it advisable to conclude that the patient's TM is likely to be monophasic as a post-vaccination phenomenon. This is not an opinion that vaccinations are irrelevant in the MS context. In the language quoted by Dr. Steel the authors simply amplify that this "low risk" is not "no risk," because they opine that vaccination can have an effect in either context. In other words, in their view the fact that a clinician concludes that an episode of TM was vaccine-caused should not in itself provide complete comfort that it will not ultimately also be the first presentation of MS. Pertinent to this point, Dr. Sriram himself indicates that the precipitating factors for MS relapse are not fully known. (Ex. O, p. 6.)

petitioner's MS and that it constituted the first clinical attack of her condition. Accordingly, petitioner has satisfied *Loving* prong three by preponderant evidence, leaving the question of whether her vaccination(s) played a causal role in that significant aggravation.

b. *Loving* Prong Four

Petitioner's burden under the first *Althen* prong / fourth *Loving* prong is to provide, by preponderant evidence, "a medical theory causally connecting the vaccination and the injury." *Althen,* 418 F.3d at 1278. Such a theory must only be "legally probable, not medically or scientifically certain." *Knudsen v. Sec'y of Human & Health Servs.*, 35 F.3d 543, 548-49 (Fed. Cir. 1994). Moreover, scientific evidence offered to establish *Althen* prong one / *Loving* prong four is viewed "not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1380 (Fed. Cir. 2009). The Federal Circuit instructs that "a paucity of medical literature supporting a particular theory of causation cannot serve as a bar to recovery." *Id*. at 1379. However, to satisfy this prong, petitioner's theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen*, 35 F.3d at 548; *Boatmon v. Sec'y of Health & Human Servs.,* 941 F.3d 1351, 1359 (Fed. Cir. 2019).

The initial ruling on entitlement in this case held that petitioner had preponderantly satisfied *Loving* prong four and discussed three factors in a more abbreviated fashion: Dr. Steel's scientific explanation of the underlying disease process; the limitations of the relevant epidemiology; and a single study by Langer-Gould, et al., that nonetheless detected at least some signal of temporary post-vaccination CNS demyelination inclusive of one of the vaccines at issue. The initial ruling characterized the Langer-Gould study as "especially relevant and persuasive." (ECF No. 73, p. 23.) On remand, however, this decision does not consider the Langer-Gould study as evidence of causation for the reasons discussed in the Court of Federal Claims' Opinion and Order. Accordingly, this decision on remand amplifies several points of analysis to explain why removing the Langer-Gould study from consideration based on the Court of Federal Claims' guidance does not ultimately change the outcome of this case upon further consideration of the record as a whole.[16]

In this case, there is no doubt that what Dr. Steel proposes as a medical theory supporting his opinion constitutes only a circumstantial case. As Dr. Sriram stresses and Dr. Steel acknowledges, no epidemiologic signal has specifically proven that vaccines can cause or significantly aggravate MS. However, it is important to note that, while Dr. Sriram notes MS patients to be a "highly studied population" (Ex. A, p. 10), the record of this case also indicates that central nervous demyelinating conditions as a

[16] Dr. Steel suggested that both vaccines – polio and Tdap – could have contributed to petitioner's condition. (Ex. 20, p. 5.) However, in his second report he focused more heavily on evidence relating specifically to the Tdap vaccine. (Ex. 54.) Thus, there is more evidence of record implicating the Tdap vaccine in autoimmune demyelination than there is for the polio vaccine. Moreover, as discussed below with regard to *Loving* prong six, the temporal relationship at issue is clearer with respect to the later Tdap vaccine than for the earlier polio vaccine. Accordingly, this decision will focus primarily on the Tdap vaccine. Having concluded petitioner has met her burden of proof with respect to that vaccine, it is not necessary to definitively resolve whether her polio vaccine may have additionally contributed to her injury.

whole are not considered to be well understood.[17] In fact, Dr. Sriram acknowledges on respondent's behalf that the ultimate cause of MS, as well as the precipitating factors for MS relapse, are considered unknown. (Ex. A, p. 8; Ex. O, pp. 6-7.) In that context, Dr. Steel's opinion constitutes the type of sound and reliable scientific explanation that can carry a case where there is a paucity of medical literature. Dr. Sriram's rebuttal offers little to no direct substantive response to the particulars of Dr. Steel's opinion. Instead, the thrust of Dr. Sriram's opinion is to assert that much of what Dr. Steel discusses is irrelevant based primarily on two points – epidemiology and "clinical prudence and parsimony" (explained further below). On this record neither of these points is persuasive as rebuttal.

i. Dr. Steel's explanation of MS autoimmunity is sound and reliable

Dr. Steel explains that MS is the most common inflammatory immune-mediated CNS demyelinating disease. (Ex. 20, p. 3.) He notes that others include TM, focal myelitis, ADEM, and neuromyelitis optica. (*Id*.) These disorders represent a "family" of conditions for which "[c]ausation is likely multifactorial, with contributing factors including genetic predisposition, environment, nutritional status, comorbidities, and exposure to various triggers." (Ex. 54, p. 2.) In that context, he proposes that MS patients are predisposed to CNS inflammation. (Ex. 20, p. 4.) He further explains that:

> Vaccines, as well as other immunogenic stressors, stimulate a heightened immune reaction in response to the antigens in the vaccines. However, this desirable response may have unintended effects by activating the immune system in the CNS, particularly in susceptible individuals such as patients with clinically asymptomatic MS, who are already undergoing an autoimmune process. Possible mechanisms include molecular mimicry, epitope spreading, bystander activation, T-helper cell activation, and cytokine induction. In a given instance, one or more of these mechanisms may be operative. Molecular mimicry is often posited as a plausible process by which vaccination could induce autoimmunity. The theory is that antibodies formed in response to the vaccine may attack myelin related epitopes if these epitopes are like the antigens in their chemical and physical structure. Although there is little evidence that vaccinations cause

[17] For example, an article filed in this case regarding the immunopathogenesis of acute TM explains in introduction that:

> Acute transverse myelitis (ATM) is a group of poorly understood inflammatory disorders resulting in neuronal injury to the spinal cord. It is unclear what are the triggers and effector mechanisms resulting in neural injury, although tantalizing clues have emerged. ATM exists on a continuum of neuroinflammatory disorders that also includes Guillain-Barre syndrome (GBS), multiple sclerosis (MS), acute disseminated encephalomyelitis and neuromyelitis optica (NMO). Each of these disorders differs in the spatial and temporal restriction of inflammation within the nervous system. However, clinical and pathological studies support the notion that there are many common features of the inflammation and neuronal injury.

(Douglas A. Kerr, Harold Ayetey, *Immunopathogenesis of acute transverse myelitis,* CURR. OP. NEUROL. 339 (2002) (Ex. 40).)

> multiple sclerosis in healthy patients, there is convincing evidence that vaccinations occasionally trigger single attacks of TM, ADEM, optic neuritis, and isolated spinal myelitis, and there is good reason to think that such an event is more likely in patients with subclinical MS.

(Ex. 20, p. 5.)

At the broadest level, the reliability of this explanation is borne out in large portion by respondent's expert's own discussion of MS. Dr. Sriram likewise explains that MS is a chronic demyelinating disorder of the CNS that results in neurologic deficits resulting from lesions affecting the optic nerves, brainstem, and spinal cord. (Ex. A, p. 7.) He also agrees that MS is generally believed to be autoimmune and that it also has an inflammatory component leading to myelitis and demyelination. He explains that

> [t]he prevailing opinion on MS is that it is mediated by T lymphocytes, which target the white matter of the central nervous system. The ongoing inflammatory response in the central nervous system results in the development of lesions in the white matter and in particular the myelin membranes of the central nervous system. Myelin is in the membranes which insulate the axons and optimize nerve conduction from one neuron to another. Loss of myelin membrane leads to impaired conduction which often results in clinical disability.

(Ex. A, p. 8.)

Further to this explanation, Dr. Steel highlights literature by Fujinami, et al., explaining what is known as the "fertile field" understanding of autoimmunity in MS. (Fujinami et al., *supra,* at Ex. 24, p. 83.) It explains why an individual already experiencing autoimmunity in the form of clinically silent MS may nonetheless be susceptible to later insults that bring about clinically apparent disease. The authors state: "[f]or example, an infection with a virus having molecular mimicry to self CNS proteins can potentially prime autoreactive T cells but not to the point where they can initiate autoimmune inflammatory CNS disease; later events may trigger these cells to cause disease." (Fujinami et al., *supra,* at Ex. 24, p. 83.) The Institute of Medicine ("IOM") has identified Fujinami's work as providing experimental evidence supporting molecular mimicry as a mechanism of autoimmunity for MS.[18] (Institute of Medicine,

[18] The Institute of Medicine (known as the National Academy of Medicine since 2015) is the medical arm of the National Academy of Sciences. The National Academy of Sciences ("NAS") was created by Congress in 1863 to be an advisor to the federal government on scientific and technical matters (*see* An Act to Incorporate the National Academy of Sciences, ch. 111, 12 Stat. 806 (1863)), and the Institute of Medicine is an offshoot of the NAS established in 1970 to provide advice concerning medical issues. When it enacted the Vaccine Act in 1986, Congress directed that the IOM conduct studies concerning potential causal relationships between vaccines and illnesses. *See* § 300aa–1 note. However, the IOM employs a standard for finding causation that is higher than what is required by petitioner's burden of proof. *E.g. Raymo v. Sec'y of Health & Human Servs.*, No. 11-654V, 2014 WL 1092274, at *21, n.39 (Fed. Cl. Spec. Mstr. Feb. 24, 2014). Accordingly, IOM reports and findings should be approached with caution. Special Masters may rely on IOM reports as evidence, but they are not dispositive. *See, e.g., Crutchfield v. Sec'y Health & Human Servs.*, 125 Fed. Cl. 251, 262 (2014) (noting that "it was appropriate for the special master to consider the medical literature presented, including the IOM report" and that "the court often has relied on the findings of the Institute of Medicine."); *See also, Isaac v. Sec'y Health &*

Adverse Effects of Vaccines: Evidence and Causality, NAT'L ACAD. SCI. 1, 71 (2012) (Ex. 66).) The "fertile field" is also considered compatible with the bystander activation mechanism additionally cited by Dr. Steel. (Fujinami et al., *supra,* at Ex. 24, p. 83.)

The Fujinami authors explain that myelin basic protein has been shown to react to a variety of viral and bacterial proteins. (Fujinami et al., *supra,* at Ex. 24, p. 81.) Based on experiments using their murine model of experimental autoimmune encephalomyelitis (EAE) (a commonly used model in the study of MS and other demyelinating conditions (*see* Neeta Garg & Thomas W. Smith, *An update on immunopathogenesis, diagnosis, and treatment of multiple sclerosis,* 5(9) BRAIN AND BEHAVIOR 1, 2 (2015) (Ex. 45); Byron Waksman & Raymond Adams, *Studies of the Effect of the Generalized Shwartzman Reaction on the Lesions of Experimental Allergic Encephalomyelitis,* 33(1) AM. J. PATHOL. 131 (1957) (Ex. 30)), Fujinami demonstrated that after a mouse clears an initial infection, even without initially producing inflammatory lesions, it is primed to produce such lesions later in life upon insult with either an adjuvant[19] or certain wild virus. (Fujinami et al., *supra,* at Ex. 24, p. 84-85.)

Respondent challenges the relevance of this paper based on the premise that it addresses only how viruses rather than vaccines can cause autoimmunity. (ECF No. 70, p. 17.) However, pertinent to Dr. Steel's reliance on this concept vis-à-vis vaccination, the Fujinami authors' findings were not limited to viral infection as they also produced results with an adjuvant. (Fujinami et al., *supra,* at Ex. 24, p. 84.) They also explained that their model predicts that the priming effect can occur following an infection occurring only in the periphery (*i.e*., not itself reaching the CNS) and can trigger CNS disease without a second infection targeting the organ in question. (*Id*. at 85.) Respondent's expert opted not to specifically address the Fujinami paper.[20] (Exs. A, O.)

Human Servs., 108 Fed. Cl. 743, 755 (2013), *aff'd,* 540 Fed. Appx. 999 (Mem.) (Fed. Cir. 2013) (affirming the special master's reliance on findings of the IOM); *Porter v. Sec'y Health & Human Servs.,* 663 F.3d 1242, 1252 (Fed.Cir.2011) (noting the special master's comment that "IOM reports are favored, although not dispositive, in the Vaccine Act Program," then affirming the special master's decision).

[19] The authors explain that "[i]n most if not all the models where molecular mimicry has been used to induce an autoimmune disease, an adjuvant such as [complete Freund's adjuvant] or an actual infection is required. This suggests that, in addition to having a cross-reacting disease, inducing epitope-sufficient activation of [antigen presenting cells] is required." (Fujinami et al., *supra,* at Ex. 24, p. 81.) An "adjuvant" is "a nonspecific stimulator of the immune system." *Adjuvant,* DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=1074 (last accessed June 6, 2022). Adjuvants are also added to some vaccines in order to increase the immune response to the vaccine. (Institute of Medicine, *supra,* at Ex. 66, p. 59.) Interestingly, the record evidence shows that the specific Tdap vaccine petitioner received was adjuvanted. (Ex. 1, p. 2 (identifying manufacturer as GSK); Ex. 58 p. 16 (package insert for GSK Boostrix describing vaccine as adjuvanted with aluminum hydroxide).) However, Dr. Steel did not specifically rely on this fact and the mechanism by which adjuvants support vaccine efficacy is not known. (Institute of Medicine, *supra,* at Ex. 66, p. 59.)

[20] Dr. Sriram's discussion of the Fujinami paper was limited to including a footnote confirming that the paper does, in fact, concern molecular mimicry, but dismissing its relevance because Dr. Steel did not in his view sufficiently address "how the molecular mimicry theory applies specifically to [petitioner's] case." (Ex. A, p. 14, n. 4.) However, this paper was cited as support for specific statements by Dr. Steel in his report indicating that non-specific immunogenic stresses, including vaccines, can trigger demyelinating

Based on their specific findings, the Fujinami authors proposed two different mechanisms of injury. (Fujinami et al., *supra,* at Ex. 24, p. 85.) First, molecular mimicry during a priming infection initially generates autoreactive T cells to a subclinical degree. Bystander activation resulting from a secondary event can then cause the autoreactive T cells to proliferate to sufficient numbers to cause disease.[21] Second, the priming infection could generate memory T cells with unrecognized cross-reactive potential. A second infection involving an antigen sharing a common epitope can expand that response and proliferate autoreactive T cells to a disease-causing level.[22] (*Id*.)

To further evidence the ability of components of the Tdap and polio vaccines to cause autoimmune injury to myelin basic protein in humans Dr. Steel relies on other vaccine-caused CNS demyelinating conditions, such as TM.[23] Specifically, Dr. Steel opined that while vaccines have not been shown epidemiologically to be an initiating cause of MS itself, "there is sufficient evidence in the medical literature to link vaccination to TM to make a biologically plausible argument for causation" (Ex. 54, p. 1) and ultimately that "the vaccine triggered an episode of spinal myelitis in the context of the patient's pre-existing clinically silent MS" (*Id*. at 7).[24] Thus, Dr. Steel relied on

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attacks in individuals suffering subclinical autoimmunity in MS. Additionally, petitioner's filing of the Fujinami paper included marking by Dr. Steel highlighting specific passages relating to the "fertile field" theory, the specific findings of the above-discussed murine study, and portions of the authors' explanation of the study's findings. (*See* ECF No. 36-4; Fujinami et al., *supra,* at Ex. 24.)

[21] Bystander activation involves "a robust or exaggerated immune response to an exogenous agent that induces local tissue inflammation and stimulation of otherwise normal unaffected cells." (Institute of Medicine, *supra,* at Ex. 66, p. 75.) This inflammation "can result in the release of normally sequestered self-antigens. The inflammation can result in nonspecific activation of previously dormant autoreactive Th1 cells that then react against newly released self-antigens." (*Id*.)

[22] Langer-Gould, et al., previously considered significant as part of the prior ruling on entitlement, similarly hypothesized based on their findings in humans that vaccinations may act in the same manner as infection to "enhance autoimmunity through expansion of autoreactive T-cell clones by molecular mimicry, later stimulation of autoreactive T-cell clones, or enhancement of antigen presentation by bystander activation . . . ." (Annette Langer-Gould et al., *Vaccines and the Risk of Multiple Sclerosis and Other Central Nervous System Demyelinating Diseases,* 71(12) JAMA NEUROL. 1506, 1511-12 (2014) (Ex. 63).)

[23] It should be noted that while petitioners do not prevail by "merely chanting the magic words 'molecular mimicry,'" *McKown v. Sec'y of Health & Human Servs*., No. 15-1541V, 2019 WL 4072113, at *50 (Fed. Cl. Spec. Mstr. July 15, 2019), it is also not the case that every petitioner citing molecular mimicry must prove the precise molecular mimic to prevail. For example, GBS caused by the flu vaccine is so widely compensated in this Program that it has been designated as a table injury, and yet, although it is assumed to occur due to molecular mimicry, the molecular mimic has not yet been identified. *See Pierson v. Sec'y of Health & Human Servs*., No. 17-1136V, 2022 WL 322836, at *23-26 (Fed. Cl. Spec. Mstr. Jan. 19, 2022) (providing extended discussion of molecular mimicry in the context of GBS). In the Vaccine Program, it is well understood that petitioners are not obligated to prove the precise mechanism of injury as a component of their causation theory. *Knudsen,* 35 F.3d at 548.

[24] A clarification regarding use of the word "plausible" may be useful. Petitioner argues that her burden under *Loving* prong four is to provide both a "biologically plausible" and "reliable" theory of causation. (ECF No. 97, p. 6.) However, the Federal Circuit has been clear in stating that "[w]e have consistently rejected theories that the vaccine only 'likely caused' the injury and reiterated that a 'plausible' or 'possible' causal theory does not satisfy the standard." *Boatmon*, 941 F.3d at 1360. Respondent likewise alludes to this point. (ECF No. 98, p. 9, n. 6.) This is not to be confused with Dr. Steel's reference to

collected case reports from review literature identifying various CNS demyelinating conditions as following certain vaccinations, specifically including both tetanus-containing and polio vaccines.[25] (Dimitrios Karussis, Panayiota Petrou, *The spectrum of post-vaccination inflammatory CNS demyelinating syndromes,* 13 AUTOIMMUNITY REVIEWS 215 (2014) (Ex. 36); N. Agmon-Levin et al., *Transverse myelitis and vaccines: a multi-analysis,* 18 LUPUS 1198 (2009) (Ex. 42); Xuan-Hung Nguyen, Abdelhadi Saoudi, Roland Liblau, *Vaccine-associated inflammatory diseases of the central nervous system: from signals to causation,* 29 CURR. OPIN NEUROL. 362 (2016) (Ex. 63).) Dr. Steel also separately cited a case report of two pregnant women who suffered optic neuritis following the Tdap vaccine. (Jose Cabrera-Maqueda et al., *Optic neuritis in pregnancy after Tdap vaccination: Report of two cases,* 160 CLIN. NEUROL. NEUROSURG. 116 (Ex. 35).) There is also some evidence of record to support a suspicion that the tetanus vaccine is implicated in autoimmune demyelination in the context of Guillain-Barré Syndrome ("GBS"), a peripheral but also demyelinating disorder. (Ex. 59, p. 3; Ex. 64, p. 4 (vaccine package inserts warning against Tdap vaccine for those who experienced GBS following prior tetanus vaccination).)

In her original motion for a ruling on the record (incorporated by reference in her supplemental brief), petitioner argued:

> Dr. Sriram attempts to dismiss these reviews and case reports with the comment that 'anecdotal accounts do not constitute evidence.' With all due respect to Dr. Sriram, this statement is incorrect. It is appropriate for this Court to take judicial notice of the fact that case reports are an accepted and longstanding feature of medical research and are routinely published in peer-reviewed medical and scientific journals. This state of affairs presumably reflects the medical community's belief that case reports provide useful information to clinicians and researchers, *i.e.*, that case reports constitute evidence.

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what is "biologically plausible," which simply expresses that the point being made is consistent with existing medical knowledge. *E.g. Doe93 v. Sec'y of Health and Human Servs.*, 98 Fed Cl. 553, 567 (2011) (collecting citations to cases where petitioners have been required to present a "biologically plausible" theory as that term is understood in the scientific community).); *accord Kottenstette v. Sec'y of Health & Human Servs.*, 861 Fed. Appx. 433, 440-41 (Fed. Cir. 2021) (assigning error where the Court of Federal Claims interpreted the special master's refence to "biologic credibility" as equivalent to the type of merely "plausible" theory presented in *Boatmon*.) A proposed theory must necessarily be biologically plausible (*i.e.*, consistent with existing medical knowledge) in order to be sound and reliable; however, biologic plausibility is not itself the legal standard. Thus, petitioner's acknowledgement that her expert's theory must be "reliable" as well as "biologically plausible" is important. According to the Federal Circuit, petitioner's expert must present an explanation in support of *Althen* prong one / *Loving* prong four that is "sound and reliable." *Boatmon,* 941 F.3d at 1359-60.

[25] While there is literature filed in this case that broadly states that vaccines in general may be a trigger of TM, there is also literature filed explaining that certain specific vaccines not at issue in this case are more strongly evidenced as causes of demyelination than others. (*E.g.*, Karussis & Petrou, *supra,* at Ex. 36; *see also* Loebermann, et al, *infra*, at Ex. 38, p. 7 (distinguishing inactivated and live attenuated vaccines).) Accordingly, general references to vaccinations as a trigger of TM must be approached with caution and the availability of evidence specifically implicating the particular vaccine(s) at issue is an important consideration.

(ECF No. 68, pp. 15-16 (quoting Ex. O, p. 4 (internal citation omitted)).)

Petitioner is correct that case reports constitute evidence and cannot be summarily rejected. "[C]ase reports 'do not purport to establish causation definitively, and this deficiency does indeed reduce their evidentiary value'…. [but] 'the fact that case reports can by their nature only present indicia of causation does not deprive them of all evidentiary weight.'" *See Paluck v. Sec'y of Health & Human Servs.,* 104 Fed. Cl. 457, 475 (2012) (quoting *Campbell v. Sec'y of Health & Human Servs.*, 97 Fed. Cl. 650, 668 (2011), *aff'd* 786 F.3d 1373 (Fed. Cir. 2015)). Thus, for example, in a prior case involving TM caused by the Tdap vaccine, a prior chief special master concluded that the rarity of TM (citing approximately 1,400 new cases diagnosed annually in the U.S.) coupled with the rarity of adult administration of the Tdap vaccine (boosters recommended only every ten years) counseled in favor of allowing greater weight to case reports involving that combination of vaccine and injury. *Raymo v. Sec'y of Health & Human Servs.*, No. 11-654V, 2014 WL 1092274, at *21 (Fed. Cl. Spec. Mstr. Feb. 24, 2014).[26]

In addition, as discussed by both the initial ruling and the Court of Federal Claims' Opinion and Order, Dr. Steel relied in his second report on a case-controlled study by Langer-Gould, et al., that found a statistically significant 30-day risk period for onset of acquired demyelinating syndromes of the CNS following various vaccinations, including Tdap. (Ex. 54, pp. 5-6 (citing Langer-Gould et al., *supra,* at Ex. 63).) Dr. Steel cited this study for the specific proposition that "within a narrow time frame after vaccination, there is an increased risk of CNS Acute Demyelinating Syndromes, including TM."[27] (Ex. 54, p. 6.) Under "conclusions and relevance" the authors stated:

[26] There is some prior track record of petitioners being awarded compensation for Tdap-caused TM; however, it has not been universally embraced. *Compare Raymo*, 2014 WL 1092274 (petitioner established entitlement to compensation for a claim alleging TM following receipt of the HPV, Hepatitis A, meningococcal, and Tdap vaccines); *Roberts v. Sec'y of Health & Human Servs.,* 09-427V, 2013 WL 5314698 (Fed. Cl. Spec. Mstr. Aug. 29, 2013) (petitioner was entitled to compensation for a claim alleging TM following receipt of the Tdap vaccine); *Helman v. Sec'y of Health & Human Servs.*, No. 10-813V, 2012 WL 1607142 (Fed. Cl. Spec. Mstr. Apr. 5, 2012) (petitioner was entitled to compensation for a claim alleging TM and NMO following receipt of the Tdap vaccine) *and, I.J. v. Sec'y of Health & Human Servs.*, No. 16-846, 2021 WL 1232733, at *29 (Fed. Cl. Spec. Mstr. Jan. 4, 2021) (noting that most Tdap/TM cases have resolved via stipulation and proffer, but distinguishing *Raymo*, *Roberts*, and *Hellman*, and denying entitlement), *rev'd* 155 Fed. Cl. 20 (2021).

[27] The study examined 780 cases of various newly diagnosed CNS demyelination syndromes, including MS (54.7% of cases), optic neuritis (22.7%), TM (15.6%), CIS (4.2%), and ADEM (2.7%). (Langer-Gould et al., *supra,* at Ex. 63, p. 1508.) They reviewed patient records for reports of any vaccine within three years prior and indicated that the most commonly reported in adults were Hepatitis B, HPV, influenza, Tdap, and varicella vaccines. (*Id*. at 1507.) The study identified 24 individuals (younger than 50) who suffered some form of a CNS demyelinating condition within 30 days of vaccination, eleven had MS, nine had optic neuritis, three had TM, and 1 had ADEM. (*Id*. at 1509.) Among those 24, eight had received the Tdap vaccine, though the study's ultimate finding was not vaccine specific. (*Id*.) As Dr. Steel explained, although different breakdowns of data by different conditions did not show any statistically significant signal, when considering all of these demyelinating conditions collectively (including MS), they observed a 30-day increased risk window among the under 50 population as compared to the controls.

> We found no longer-term association of vaccines with MS or any other [acquired central nervous system demyelinating syndromes], which argues against a causal association. The short-term increase in risk suggests that vaccines may accelerate the transition from subclinical to overt autoimmunity in patients with existing disease. Our findings support clinical anecdotes of [acquired central nervous system demyelinating syndromes] symptom onset shortly after vaccination but do not suggest a need for a change in vaccine policy.

(Langer-Gould et al., *supra,* at Ex. 63, p. 1506.) Thus, petitioner contends in effect that, by the study authors' own conclusion, the Langer-Gould study bolsters the validity of prior case reports of post-vaccination CNS demyelination, such as those cited by Dr. Steel, and suggests that epidemiology examining an overall causal relationship between MS and vaccines is not dispositive regarding the question of significant aggravation. The initial ruling on entitlement characterized the Langer-Gould study as "especially relevant and persuasive" as a crystallization of Dr. Steel's theory because it included a statistically significant finding of post-vaccination acquired CNS demyelinating syndromes in humans that implicated the Tdap vaccine and included an explanation of its findings by the study authors mirroring the "fertile field" understanding of autoimmunity underlying Dr. Steel's own opinion in this case. (ECF No. 73, pp. 23-25.)

On review, however, the Court of Federal Claims assigned error in the initial ruling's consideration of the Langer-Gould study. The Court looked at the fact that no association was found when MS was viewed in isolation, the fact that no association was found for the over 50 group, and the fact that onset of petitioner's own condition was outside the 30-day risk window identified by the study. Accordingly, the Court indicated that "there is no way to look at the data and find an association between vaccinations and Petitioner's own condition." (ECF No. 90, p. 8.) The Court further indicated that "[a]lthough there can be association without causation, there cannot be causation without association." (*Id*.)

Nonetheless, petitioner continues to argue in her supplemental brief on remand that the Langer-Gould study should carry some evidentiary weight. Specifically, petitioner contends that "the authors of the study themselves appear to believe that their findings are of general applicability when it comes to vaccinations and CNS disease, including MS. Dr. Steel is simply re-iterating their conclusion and applying it to the instant case – an application that their wording plainly allows." (ECF No. 97, p. 16.)

The Court remanded the case with the instruction "to re-evaluate the medical evidence under the correct legal and scientific standards." (ECF No. 90, p. 10.) However, the Court also made explicit findings regarding the Langer-Gould study itself that preclude it from further consideration. The Court highlighted language from *Broekelschen v. Secretary of Health and Human Services,* instructing that a petitioner must provide "a reputable medical or scientific explanation that pertains specifically to the petitioner's case[.]" (ECF No. 90, pp. 3, 9 (quoting 618 F.3d 1339, 1345 (Fed. Cir.

(*Id*. at 6 (Figure 2).) The authors indicated that a limitation of the study was that "the number of older individuals was relatively small." (*Id*. at 7.)

2010).) The Court concluded that "[t]he fact that the Langer-Gould study shows no association relevant to Plaintiff means that it does not evidence causation: A finding of causation would have to be *despite* the Langer-Gould study, not *because* of it." (*Id*. (emphasis original).) Thus, although this decision on remand otherwise re-evaluates the medical evidence as a whole in accordance with the Court's remand instruction, it adopts the Court's specific finding that the Langer-Gould study does not evidence causation as the law of the case.[28]

Given that the Langer-Gould study – at least by petitioner's and Dr. Steel's account – bolstered the value of prior case reports regarding post-vaccination CNS demyelination, removing the study from consideration does leave this a closer case. However, Langer-Gould was never the sole support for Dr. Steel's theory. In fact, it was not even cited until he submitted his second report. In any event, "[t]he Vaccine Act does not contemplate full blown tort litigation in the Court of Federal Claims. The Vaccine Act established a federal 'compensation program' under which awards are to be 'made to vaccine-injured persons quickly, easily, and with certainty and generosity.'" *Knudsen*, 35 F.3d at 549 (quoting H.R.Rep. No. 99–908, 99th Cong., 2d Sess. 18, *reprinted in* 1986 U.S.C.C.A.N. 6344.) Accordingly, the Federal Circuit has suggested that this program represents a "system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants." *Althen*, 418 F.3d at 1280.

Even without the Langer-Gould study, Dr. Steel's explanation of the underlying immunology remains sound and reliable and preponderantly establishes that vaccines, including Tdap, can significantly aggravate subclinical MS to produce demyelinating lesions. Important to this point, Dr. Sriram likewise acknowledges that MS relapses are known to respond to immune precipitating factors such as intercurrent infections and abrupt withdrawal of immune modulating therapies. (Ex. O, pp. 6-7.) Although Dr. Sriram does not extend this conclusion beyond these two established triggers, he acknowledges that ultimately the cause(s) or precipitating factors of MS relapses otherwise remain unknown. (*Id*.) In that regard, Dr. Steel's filing of a meta-analysis by Mohr, et al., provides evidence going beyond what Dr. Sriram readily accepts and further suggests, as Dr. Steel contends, that the stimuli at issue with specific regard to MS relapse can be non-specific immunogenic stresses beyond active infection.[29] (Ex.

[28] Law of the case is a judicially created doctrine, the purpose of which is to prevent relitigation of issues that have been decided. *See Gould, Inc. v. United States,* 67 F.3d 925, 927–28 (Fed.Cir.1995). The Federal Circuit has confirmed that the law of the case doctrine applies in Vaccine Act cases. *Suel v. Sec'y of Health & Human Servs.*, 192 F.3d 981 (Fed. Cir. 1999). Respondent also argued substantively that the decision on remand cannot rely upon the Langer-Gould study but did not specifically cite the law of the case doctrine. (ECF No. 98, pp. 8-9.) Because I am following the law of the case, I do not reach respondent's substantive arguments on remand regarding Langer-Gould. I do note, however, that respondent's argument generally repeats the analysis contained in the Court's Opinion and Order.

[29] The Mohr authors hypothesize that reducing stress in people with MS can reduce T cell production, suggesting based on prior animal studies that increases in stress-related cortisol may enhance sensitivity to proinflammatory T cells. (Mohr et al., *supra,* at Ex. 44, p. 3.) Even setting aside that specific hypothesis, this meta-analysis provides some indication in humans that the course of MS attacks respond to stimuli as Dr. Steel explains, though the authors caution that "the occurrence of any specific exacerbation cannot yet be linked to any specific stressor." (*Id*. at 4.)

20, p. 4; *see also* David C. Mohr et al., *Association between stressful life events and exacerbation in multiple sclerosis: a meta-analysis,* BMJ 1 (2004) (Ex. 44).) Further, Dr. Steel cites to researchers who have included statements in their papers expressing views consistent with the theory offered by Dr. Steel in this case. (Frohman & Wingerchuk, *supra,* at Ex. 39, p. 567 ("The occurrence of transverse myelitis after infection or vaccination does not preclude the need for further evaluation, since infection or immunization may also trigger attacks of myelitis in the context of an underlying disease (especially multiple sclerosis or neuromyelitis optica)."); Langer-Gould, *supra,* at Ex. 63, p. 1512 ("our findings are consistent with vaccines acting as a proinflammatory cofactor in individuals with subclinical autoimmunity because this mechanism would be expected to hasten symptom onset but not change the long-term risk of developing MS or CIS."[30]); Kerr and Ayetey, supra, at Ex. 61, p. 344 ("emerging evidence suggests that *a variety of immune stimuli, through such processes as molecular mimicry* or superantigen-mediated immune activation, may trigger the immune system to injure the nervous system. *The activation of previously quiescent autoreactive T lymphocytes* or the generation of humoral derangements may be effector mechanisms in this process." (emphasis added)).)

ii. Dr. Sriram is unpersuasive in rebuttal

As noted above, the affirmative case presented by petitioner in support of her prima facie burden under *Loving* prong four is a close call. Accordingly, the lack of persuasiveness in Dr. Sriram's response is a significant factor further contributing to the outcome in this case. Dr. Sriram's rebuttal to Dr. Steel's theory is primarily grounded in two points – the lack of epidemiologic support and "clinical prudence and parsimony." Neither is persuasive on this record. I address each in turn.

1. Epidemiology

Dr. Sriram agrees that the underlying premise of Dr. Steel's theory has been a relevant concern in the medical community and that a causal role for vaccinations has been suspected in the worsening of MS. Specifically, he explains that "[s]ince vaccines are proteins and are given to induce an immune response to deter bacterial and viral infections, there was concern that introducing antigens into the body could worsen autoimmune diseases, including multiple sclerosis." (Ex. A, p. 9.) However, based on his review of relevant epidemiology, Dr. Sriram takes the view that this concern was not ultimately borne out. (*Id*. at 9-10.)

The Federal Circuit has previously stressed that a petitioner is not obligated to present an epidemiological case supporting her claim. *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1325 (Fed. Cir. 2006). Nonetheless, "[n]othing in *Althen* or *Capizzano* requires the Special Master to ignore probative epidemiological evidence that undermines petitioner's theory." *D'Tiole v. Sec'y of Health & Human Servs.*, 726 F. App'x 809, 811 (Fed. Cir. 2018) (citing *Andreu*, 569 F.3d at 1379 ("Although *Althen* and *Capizzano* make clear that a claimant need not produce medical literature or

[30] Though noting the expressed views of the authors, this study itself does not support causation for the reasons discussed above.

epidemiological evidence to establish causation under the Vaccine Act, where such evidence is submitted, the Special Master can consider it in reaching an informed judgment as to whether a particular vaccination likely caused a particular injury."). Here, however, the epidemiology at issue has significant limitations, which Dr. Steel has addressed, and does not ultimately undermine petitioner's theory.

Dr. Steel agrees that the epidemiological evidence indicates that "MS, a chronic, recurrent and progressive disorder, is not likely caused by any single immune insult event." (Ex. 20, p. 4.) However, Dr. Steel also cautioned that "since all vaccine injuries are quite rare relative to the total number of vaccinations administered . . . [i]t is possible for a given adverse event to occur, but not to occur with sufficient frequency to produce an epidemiological signal." (Ex. 54, p. 7.) He also opined that "[t]he dissemination of MS clinical events in time means that relating onset of symptoms to specific immune challenges is difficult, and it is likely that triggering of clinically significant MS by vaccine is underreported for this reason." (Ex. 20, p. 4.) Mailand and Fredericksen, a literature review on vaccines and MS that is often cited as authoritative and was relied upon by Dr. Sriram in this case, agrees, noting that:

> Another problem of studying MS risk factors is the lag between onsets of the initial symptoms and final diagnosis. Time between symptoms and diagnosis varies considerably depending on several factors, including individual health-seeking behaviour, health care systems, diagnostic techniques, etc. As a result, studies with short follow-up have a risk of disregarding potential association. However, studies with a too long follow-up risk diluting a potential association or to find false positive association due to subsequent triggers. Finally, manifestations of MS vary significantly between patients, making it difficult to compare the course of the disease.

(Mia T. Mailand & Jette L. Frederiksen, *Vaccines and multiple sclerosis: a systematic review,* 264 J. NEUROL. 1035, 1048 (2017) (Ex. E).)

Mailand and Fredericksen note in their conclusion that accumulated evidence so far does not find an association between a number of vaccines, including tetanus-containing vaccines, and MS relapses, but ultimately indicate that an association cannot be fully excluded without further research. (*Id.*) Dr. Sriram cited one study that post-dated the Mailand and Frederickson review; however, that study was not able to reach any conclusion with respect to tetanus-containing vaccines specifically.[31] (Alexander Hapfelmeier et al., *A large case-control study on vaccination as risk factor for multiple sclerosis,* 93(9) NEUROLOGY e908 (2019) (Ex. J).) Many of the earlier epidemiologic studies were previously addressed by the IOM in its 2012 report. As of 2012, the Institute of Medicine concluded that epidemiologic evidence is "insufficient or absent" to assess whether there is an association between diphtheria toxoid or acellular pertussis

[31] When discussing the effects of specific vaccinations, the authors explained that "[s]ufficient numbers for meaningful analysis were available for vaccinations against TBE virus, HPV, pneumococci, meningococci, influenza, hepatitis A and B, meningococci [sic], MMR, and varicella viruses[,]" *i.e.* not tetanus-containing vaccines. (Hapfelmeier et al., *supra,* at Ex. J, p. e912.)

vaccine and either onset or relapse of MS in adults. (Institute of Medicine, *supra,* at Ex. 66, p. 583.)

In his response to petitioner's original motion for a ruling on the written record (incorporated by reference in his supplemental brief), respondent contended: "[f]or example, in Exhibit 28, Loebermann et al. affirm that 'a recent extensive review from the US Institute of Medicine' *debunked* '[c]oncerns . . . that . . . vaccination might [] trigger the onset of MS in susceptible individuals.'" (ECF No. 70, p. 20 (emphasis added) (quoting Ex. 28, p. 1).) However, respondent's incomplete quotation from Loebermann misstates the IOM's conclusion. The Loebermann article itself accurately states that "[t]he US Institute of Medicine did not find sufficient evidence to accept *or reject* a causal relationship between onset of MS and vaccination against [various vaccinations]." (Micha Loebermann et al., *Vaccination against infection in patients with multiple sclerosis,* NATURE REVIEWS NEUROL. 143 (2012) (Ex. 28) (emphasis added).) The finding by the IOM that the available evidence is insufficient to reject a causal relationship explicitly contradicts respondent's framing of the report as "debunking" petitioner's theory. With specific regard to tetanus-containing vaccinations, two of the four studies cited by Loebermann, et al. – DeStefano (Loebermann ref. 15) and Confraveux (Loebermann ref. 16), both discussed below – have been separately filed in this case and contributed to the 2012 IOM review that concluded a causal relationship could not be rejected.

In particular, respondent urged that "original research by DeStefano et al. *refuted* the theory that 'exposures that occur shortly before initial clinical symptoms,' e.g., vaccinations, 'would be most likely acting as triggers of clinical disease expression in individuals who already have an underlying disease process,' e.g., MS." (ECF No. 70, p. 20 (quoting Ex. 34, p.4) (emphasis original).) However, the IOM concluded that this DeStefano study "lacked validity and precision" and noted that it had specific limitations in how it addressed timing and failed to include a short-term assessment in its primary analysis. The IOM indicated it had "limited confidence in the epidemiologic evidence" addressing onset or relapse of MS in adults following tetanus containing vaccines. (Institute of Medicine, *supra,* at Ex. 66, p. 549-51.) This conclusion also included review of the additional Confavreux, et al, study cited by Loebermann and stressed by Dr. Sriram in his second report.[32] (Institute of Medicine, *supra,* at Ex. 66, p. 549-51); *see also* Ex. O, p. 7 (citing Christian Confavreux et al., *Vaccinations and the Risk of Relapse in Multiple Sclerosis,* 344(5) N.E. J. MED. 319 (Ex. P)).)

Dr. Sriram goes still further, stressing that certain of the prior epidemiologic studies suggest not only the lack of any association but instead that tetanus vaccine has

[32] In his supplemental brief, respondent stresses that the initial ruling on entitlement characterized the Confavreaux study as having been cited by Dr. Sriram. (ECF No. 98, p. 10, n. 8.) Respondent notes instead that Dr. Steel cited the study first. (*Id.*) However, Dr. Sriram did not merely respond to Dr. Steel's initial citation, he affirmatively cited it as rebuttal to Dr. Steel's separate reliance on the above-discussed Frohman and Wingerchuk paper. (Ex. O, p. 4.) In any event, there can be absolutely no question that it is ultimately respondent rather than petitioner relying on the body of epidemiology regarding vaccines and MS. Thus, any short-comings apparent in the study necessarily have more impact on respondent's arguments.

a protective effect against MS.[33] (Ex. A, pp. 9-10.) He similarly stresses that "[a]s clinicians we don't withhold immunizations on the belief that [vaccinations] may 'trigger' relapses in MS patients." (Ex. A, p. 15.) This is confounded by the possibility of infection being the more significant risk as compared to vaccination. (*See, e.g.*, Loebermann et al., *supra,* at Ex. 28, p. 149 (explaining that "[a]voidance of infection in patients with MS generally reduces the risk of relapse and deterioration of health status . . ."). That vaccines protect against the still greater risk of infection does not mean that they are themselves entirely risk free. Thus, for example, Mailand and Fredericksen explain that "[i]n general, it seems that more benefits than costs are associated with vaccination of MS patients. First and foremost to evade potential life-threatening diseases, but also to avoid infections that might accelerate progression of the disease." (Mailand & Frederiksen, *supra,* at Ex. E, p. 1048.) They identify the *potential* protective effect of tetanus vaccination but explain that many of the relevant studies lack statistical power or contain confounding factors. (*Id.* at 1046.) They conclude that the protective effect "might exist" but that further study is necessary. (*Id.*)

Thus, despite the lack of any clear epidemiologic signal, and contrary to Dr. Sriram's suggestion that concern regarding vaccine-related worsening of MS is only a past tense concern, the medical literature filed in this case shows that researchers in the relevant field continue to consider this an open question unresolved by epidemiology. While some of the literature filed does include stronger language purporting to rule out vaccines as causally important (*e.g.*, Loebermann et al., *supra,* at Ex. 28, p. 149), when considering the record as a whole Dr. Sriram is unpersuasive in his suggestion that there is a "prevailing view" in the relevant medical community that epidemiology precludes petitioner's claim. (Ex. A, p. 9.)

2. Clinical prudence and parsimony

Apart from epidemiology, the crux of Dr. Sriram's critique of Dr. Steel's opinion is the assertion that Dr. Steel's reliance on evidence relating to acute TM in the context of MS is unreasonable "conflation." (Ex. O, p. 3.) Dr. Sriram opines that "[w]hen a neurological syndrome like spinal myelitis is a well-defined part of the clinical picture of a given disease, e.g., MS, it is clinical prudence and parsimony (Occam's Razor)[34] to recognize that the clinical picture is more than likely to be due to the underlying disease process, i.e., MS, than some other cause." (*Id*. at 1-2.) He also asserts that Dr. Steel

[33] Dr. Sriram has previously presented this logic and it has been rejected. *Jane Doe/74 v. Sec'y of Health & Human Servs.*, No. [Redacted], 2010 WL 2788239, at *9 (Fed. Cl. Spec. Mstr. June 28, 2010) (explaining that "[Dr. Sriram] noted that Hernán and his co-authors in respondent's Exhibit C–5 did a meta-analysis of studies showing a decreased risk of MS among those who received tetanus vaccine but were unable to explain why [*sic*.] the reasons for this. If this result is accurate, it does not mean that no one who receives tetanus vaccine can get MS. It just means the risk is less.")

[34]"Occam's razor is "[t]he principle of parsimony. William of Occam (14th century) stated it thus: 'The assumptions introduced to explain a thing must not be multiplied beyond necessity." *Fisher v. Sec'y of Health & Human Servs.,* 99-432V, 2009 WL 2365459, at n. 6 (Fed. Cl. Spec. Mstr. July 13, 2009) (quoting Stedman's Medical Dictionary 27th ed. (2000) at 1250.)

"seeks to collapse the well-accepted distinction between idiopathic transverse myelitis and disease-associated transverse myelitis . . . ." (*Id*. at 6.) However, in the context of this case, this critique is unpersuasive without more and inconsistent with petitioner's burden of proof.[35]

Dr. Steel observes that among all CNS demyelinating conditions "[t]he disorders differ in epidemiology (*i.e*., age and sex predilection), and clinical factors such as speed of onset, diversity of symptoms, severity of attacks, outcome, and prognosis." (Ex. 20, p. 4.) However, he explains that "[t]hese disorders are all acquired diseases of the white matter of the central nervous system caused by self-directed attack by both humoral and cellular immune elements." (*Id*.) He further indicates that CNS demyelinating disorders "share common histopathological findings on microscopic study of damaged tissue including perivenular extravasation of inflammatory cells (lymphocytes, monocytes), destruction of astrocytes and myelin sheaths, proliferation of microglia, and accumulation of antibodies and mediator of inflammation in a spotty or sometimes diffuse fashion in the CNS white matter." (*Id*. at 3-4.)

That is, according to Dr. Steel, relapsing MS, though having distinct features of its own, still includes discrete episodes of immune-related, inflammatory demyelination likely occurring as the result of the same immune process as other CNS demyelinating conditions and causing the same type of damage as seen in those other conditions. Thus, for example, the TM Consortium Working Group, discussed with respect to *Loving* prong three above, stressed the importance of distinguishing idiopathic ATM from disease-associated ATM for purposes of medical treatment and improved care, but, consistent with Dr. Steel's opinion, also nonetheless observed that "the inflammatory pathologies of MS, ADEM, and NMO may exist on a continuum with ATM." (TM Consortium Working Group, *supra,* at Ex. 68, p. 501.) Indeed, the gravamen of much of the literature addressing diagnosis is that a first attack of MS cannot always be clinically distinguished from TM upon initial presentation. In fact, Dr. Sriram himself

[35] It must be stressed here that Dr. Sriram's specific statement favoring clinical parsimony is part of an overarching opinion that charges Dr. Steel with a "mistake in clinical diagnosis" regarding the invocation of TM in a patient with MS. (Ex. O, p. 6.) In some contexts, clinical parsimony or Occam's razor can be invoked with specific regard to choosing among diagnoses. *E.g. Fisher*, 2009 WL 2365459, at *15 (explaining Dr. Sriram's use of clinical parsimony with specific respect to identifying a unifying diagnosis to explain all symptoms). And, as discussed regarding *Loving* prong three above, it is clear that Dr. Sriram is correct to the extent that petitioner cannot be diagnosed with a separate APTM. However, the specific question of diagnosis is not the limit of what Dr. Sriram contends in this case. Dr. Sriram also explained that "Dr. Steel's statement, '[a]cute partial transverse myelitis is strongly associated with Multiple Sclerosis either as an initial presenting disease or as part of the ongoing relapsing-remitting course of MS' is in agreement with my position that [petitioner] in fact presented with a myelitic picture compatible with her MS diagnosis . . . the initial presentation of an inflammatory demyelinating condition like TM becomes a feature of MS once the MS diagnosis is made; it does not remain a separate disease *for which there is no clear etiology*." (Ex. O, p. 3 (emphasis added).) Later in the same report Dr. Sriram states that "Dr. Steel's argument that 'very likely, the immune stimulation from multiple vaccinations altered her biologic equilibrium,' resulting in an 'unmasking' of [petitioner's] MS, lacks any scientific foundation and contravenes what we know about MS as a disease process." (*Id*. at 6.) Thus, it is clear that Dr. Sriram's point is not only that the APTM diagnosis should not be separately applied. He also contends that the MS disease process provides a "clear etiology" and should itself be considered explanation enough for the myelitic event at issue. This section discusses why this further assertion is unpersuasive.

quotes literature characterizing MS as "often 'indistinguishable [from transient demyelinating syndromes] at the time of initial presentation.'" (Ex. O, p. 3 (quoting Lauren B. Krupp, Brenda Banwell, Silvia Tenembaum, *Consensus definitions proposed for pediatric multiple sclerosis and related disorders,* 68 NEUROL. 1, 1-3 (2007) (Ex. L).)

Although Dr. Sriram provides a competing view that scientific evidence regarding the causes of acute TM is not at all relevant in the context of MS, his written opinion offers little to substantiate that view. In fact, he otherwise acknowledges on respondent's behalf that MS is an inflammatory and autoimmune demyelinating condition for which "ultimately the cause of the disease remains unknown." (Ex. A, p. 8.) RIS quite often leads to an eventual clinical manifestation of MS, but it is not inevitable. One study filed in this case found that 84% of patients with RIS findings in the spinal cord progressed to CIS. (*See* D.T. Okuda et al., *Asymptomatic spinal cord lesions predict disease progression in radiologically isolated syndrome,* 76 NEUROL. 686 (2011) (Ex. 46).) However, that same study indicated that only 7% of patients with RIS without cervical spinal involvement, like petitioner prior to vaccination, progressed to CIS. (*Id*. at 690.) The literature filed in this case also explains that "[t]he absence of a relation between relapses and irreversible disability suggests that there is a dissociation at the biologic level between recurrent acute focal inflammation and progressive degeneration of the central nervous system." (Christian Confavreux et al., *Relapses and Progression of disability in Multiple Sclerosis,* 343(20) N.E. J. MED. 1430, 1437 (2000) (Ex. 29).) Thus, Dr. Sriram offers only that "[r]elapses are a central feature of MS and their occurrence &/or factors precipitating it are not known." (Ex. O, p. 6.)

Dr. Sriram's written opinion also lacks any specific challenge to Dr. Steel's broader assertion that MS attacks are affected by external factors and immune stimuli. In fact, he acknowledges that intercurrent infections and abrupt withdrawal of immunomodulatory medication are examples of immune-related triggers that *do* cause relapses. (*Id*. at 6-7; *see also* Nathan Young, Brian G. Weinshenker, Claudia F. Lucchinetti, *Acute Disseminated Encephalomyelitis: Current Understanding and Controversies,* 28(1) SEMIN. NEUROL. 84, 86-87 (2008) (Ex. M) (noting patients with a first presentation of MS as having increased frequency of antecedent infections)). Additionally, as explained above, Mohr, et al., provides at least some support for the proposition that the course of MS exacerbations responds to stimuli beyond those acknowledged by Dr. Sriram. (Mohr et al., *supra,* at Ex. 44.)

Dr. Sriram stresses that Dr. Steel's own citations support the distinction between disease-caused and idiopathic TM. (Ex. O, p. 6.) Respondent likewise stresses that demyelinating diseases are not interchangeable. (ECF No. 98, p. 13, n. 15 (citing *Chen v. Sec'y of Health & Human Servs*., No. 16-634V, 2019 WL 2121208).) This is undoubtedly true, as is made is clear by the above discussion relative to *Loving* prong three. The distinction clearly has meaning in terms of prognosis and treatment, but these conditions are not entirely unrelated for the reasons discussed by Dr. Steel. The necessary further question is what, if any, significance the distinction between idiopathic and disease-associated TM ultimately has regarding the underlying pathophysiology and potential cause(s) and/or trigger(s). To be persuasive, respondent and his expert would need to substantiate the implicit assertion that the differences among related

demyelinating conditions are more important to the analysis of petitioner's causal theory than the commonalities. That has not been done here.[36]

Dr. Sriram contends of Dr. Steel's supporting citations that "one of the papers which he presents (Exhibit 54, reference 3, Exhibit 61) clearly distinguishes between disease-associated TM and putative 'postvaccination' TM, which is categorized as a type of idiopathic TM." (Ex. O, p. 4.) Dr. Sriram explains that this paper describes the immunopathogenesis of TM as "varied" and further explains that TM associated with MS includes "perivascular lymphocytic cuffing and mononuclear cell infiltration immunopathogenically and with variable complement and antibody deposition." (*Id*. (quoting Douglas A. Kerr, Harold Ayetey, *Immunopathogenesis of acute transverse myelitis,* CURR. OP. NEUROL. 339, 340 (2002) (Ex. 61).) Significantly, however, the purpose of that quoted language is to distinguish MS-related TM from *other disease-associated TM* related to lupus, thrombotic infarction, and neurosarcoid-associated non-caseating granulomas. (*Id.* at 340.) The article goes on to explain that all are "poorly understood" and that the article will simply focus on idiopathic acute TM. (*Id*.) This is the only attempt Dr. Sriram offers to physiologically distinguish MS-associated TM from idiopathic TM. Yet nowhere in Dr. Sriram's report does he explain why the features identified (*i.e*. lymphocytic cuffing and mononuclear cell infiltration, as well as complement and antibody deposition) should be viewed as incompatible with a vaccine-triggered immune response leading to disease-associated TM. Rather, Dr. Sriram points again to the fact that this paper notes there is no associational evidence linking

[36] It is important to note that while the relevance of each article is not a given, special masters are obligated to consider the record as a whole and petitioners must be permitted to prove their cases circumstantially. *Althen*, 418 F.3d at 1280 (citing *Knudsen,* 35 F.3d at 549). It is not necessarily unusual for experts to rely in part on evidence pertaining to separate, but related, conditions. *E.g. Patton v. Sec'y of Health & Human Servs*., No. 15-1553, 157 Fed. Cl. 159 (2021) (reversing the special master where the special master rejected petitioner's expert's reliance on evidence relating to GBS to show that the flu vaccine can cause brachial neuritis.); *Koller v. Sec'y of Health & Human Servs*., No. 16-439, 2021 WL 5027947 (Fed. Cl. Spec. Mstr. Oct. 8, 2021) (special master finding petitioner established Prevnar vaccine can cause GBS where a key piece of evidence was a study about MS). Thus, given Dr. Steel's explanation (supported by record evidence) that demyelinating diseases, including MS, idiopathic TM, and disease-associated TM, represent a family of pathophysiologically related conditions, respondent does not defeat petitioner's claim merely by declaring that the conditions are not "interchangeable" and therefore contending that only literature strictly addressing MS may be considered. In fact, although CNS demyelinating conditions are not all the same, in some prior instances the precise diagnosis has not been treated as dispositive of the causation analysis. *E.g.*, *Hitt v. Sec'y of Health & Human Servs.,* No. 15-1283V*,* 2020 WL 831822, at n.8 (Fed. Cl. Spec. Mstr. Jan. 24, 2020) (finding preponderant evidence of an initial diagnosis of TM followed by a subsequent diagnosis of multiple sclerosis, but noting that "the importance of the diagnosis is diminished" by respondent's expert's agreement that either condition can be caused by the flu vaccine.); *Jane Doe/74,* 2010 WL 2788239, at *10 (finding that "[p]etitioner has fulfilled the first *Althen* prong by proving through Dr. Smith's testimony that an antigen in diphtheria/tetanus or MMR can cause demyelinating disease, such as TM/MS, through an autoimmune process . . ."). The *Althen* petitioner herself suffered optic neuritis that was part of a broader a CNS demyelinating disorder without a clear diagnosis. *Id*. at 1276-77. The Federal Circuit upheld the Court of Federal Claims' conclusion that the petitioner had met her burden where, *inter alia*, her expert opined that "in his judgment, whether petitioner's condition is diagnosed as relapsing ADEM, MS, or CNS vasculitis 'is not a big issue' as 'the underlying inflammatory process is undoubtedly the same in each instance.'" *Althen v. Sec'y of Health & Human Servs*., 58 Fed. Cl. 270, 276-77 (2003).

vaccinations and increased incidences of neurological complications, a point which is addressed separately above.[37] (Ex. O, p. 4.)

It is conceivable that Dr. Sriram could have persuasively developed these points given that prior MS cases in this program have been presented to mixed results.[38] On this record, however, Dr. Steel is persuasive in suggesting that the causes of MS relapses are multifactorial. (Ex. 54, p. 2.) Accordingly, without more, labeling petitioner's attack of myelitis as an MS relapse is not an answer that precludes vaccine causation as Dr. Sriram proposes. That is, it does not preclude other contributing causal factors apart from the MS itself and does not in itself persuasively suggest that Dr. Steel is engaged in unreasonable conflation when he considers the causes of acute TM as evidence supportive of what may likewise trigger comparable demyelination in the context of a relapse in MS.

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[37] The Kerr article is not itself informative of whether these distinctions are ultimately significant for purposes of causation, and it should be further noted that the article stresses in the introduction that TM and MS exist on a continuum of neuroinflammatory disorders and that "clinical and pathological studies support the notion that there are many common features of the inflammation and neuronal injury" among these conditions. (Kerr and Ayetey, *supra*, at Ex. 61, p. 339.) The authors specifically note that for all of these conditions there are outstanding "critical questions that must be answered before we truly understand acute transverse myelitis." (*Id.*) Among these questions, the authors highlight "What are the various triggers for the inflammatory process that induces neuronal injury in the spinal cord?" (*Id.*) However, in their conclusion the authors posit without respect to any specific diagnosis that: "emerging evidence suggests that *a variety of immune stimuli, through such processes as molecular mimicry* or superantigen-mediated immune activation, may trigger the immune system to injure the nervous system. *The activation of previously quiescent autoreactive T lymphocytes* or the generation of humoral derangements may be effector mechanisms in this process." (*Id.* at 344 (emphasis added).) This hypothesis is consistent with Dr. Steel's reliance on the fertile field theory for this case, as cited separately above.

[38] *See Robinson v. Sec'y of Health & Human Sers.,* No. 14-952V, 2021 WL 2371721 (Fed. Cl. Spec. Mstr. Apr. 12, 2021) (finding flu vaccine caused MS); *Hitt v. Sec'y of Health & Human Servs*., No. 15-1283V, 2020 WL 831822 (Fed. Cl. Spec. Mstr. Jan. 24, 2020) (finding that the flu vaccine caused petitioner "to develop transverse myelitis and, ultimately, multiple sclerosis"); *Quackenbush-Baker v. Sec'y of Health & Human Servs.*, No. 14-1000V, 2018 WL 1704523, at *17-19 (Fed. Cl. Spec. Mstr. Mar. 14, 2018) (finding flu vaccine significantly aggravated MS); *Smith v. Sec'y of Health & Human Servs.*, No. 08–864V, 2016 WL 2772194 (Fed. Cl. Spec. Mstr. Apr. 18, 2016) (awarding compensation for MS linked to a hepatitis B vaccine); *Fisher v. Sec'y of Health & Human Servs.*, No. 99-432V, 2009 WL 2365459 (Fed. Cl. Spec. Mstr. July 13, 2009) (same); *Werderitsh v. Sec'y of Health & Human Servs*., No. 99–310V, 2006 WL 1672884 (Fed. Cl. Spec. Mstr. May 26, 2006) (same); *but see W.C.*, 704 F.3d 1352 (affirming special master's decision denying entitlement for MS significantly aggravated by flu vaccine). Tetanus has also been implicated as causally contributing to MS injury in connection with other vaccines, but not in isolation. *Giannetta v. Sec'y of Health & Human Servs.*, No. 13-215V, 2017 WL 4249946 (Fed. Cl. Spec. Mstr. Sept. 1, 2017) (MS found to be caused by meningococcal vaccine based on tetanus toxoid component of the vaccine); *Jane Doe/74 v. Sec'y of Health & Human Servs.*, No. [Redacted], 2010 WL 2788239 (Fed. Cl. Spec. Mstr. June 28, 2010) (awarding compensation for TM and MS linked to tetanus-diphtheria and measles-mumps-rubella ("MMR"), hepatitis B, and meningococcal vaccines); *but see Pek v. Sec'y of Health & Human Servs.*, No. 16-736V, 2020 WL 1062959 (Fed. Cl. Spec. Mstr. Jan. 31, 2020) (denying entitlement where petitioner alleged flu and Tdap vaccines caused MS); *Bubb v. Sec'y of Health & Human Servs.*, No. 01-721V, 2005 WL 1025707 (Fed. Cl. Spec. Mstr. Apr. 29, 2005).

In the context of a significant aggravation claim, petitioner is obligated to demonstrate as a matter of specific causation that her vaccination(s) *affected* her condition rather than having *initially caused it* and will not have any burden to prove that her ultimate condition is worse than her expected outcome. *Sharpe v. Sec'y of Health & Human Servs*., 964 F.3d 1072, 1081 (Fed. Cir. 2020). Thus, in terms of presenting a medical theory of general causation, the Federal Circuit has explained that "[u]nder *Loving* prong 4, a petitioner need only provide 'a medical theory causally connecting [petitioner]'s significantly worsened condition to the vaccination.' In other words, Petitioner was required to present a medically plausible theory demonstrating that a vaccine 'can' cause a significant worsening of [petitioner's injury]." *Sharpe*, 964 F.3d at 1083 (citing quoting *Loving*, 86 Fed. Cl. at 144 (internal citation omitted).) Thus, the Circuit emphasized that "a petitioner may be able to make out a prima facie case under *Loving* prong 4 without eliminating a preexisting condition as the cause of her significantly aggravated injury."[39] *Id*. at 1083.

In the context of this case, the *Sharpe* holding suggests that while it could be *potentially* relevant that the demyelinating episode at issue is ultimately attributable to petitioner's ongoing MS, that fact is not necessarily dispositive, as Dr. Sriram urges. In light of all of the above, Dr. Sriram is not persuasive in asserting that clinical parsimony dictates that a patient's MS is itself the only relevant causal factor in any given instance of MS-related CNS demyelination or that the causes of other CNS demyelinating conditions are wholly irrelevant to determining the triggers of MS attacks. In that context, adopting Dr. Sriram's tact of clinical parsimony would impermissibly heighten petitioner's burden of proof. According to *Sharpe*, petitioner is not obligated to provide a theory under *Loving* prong four that entirely rules out her MS as causally relevant. Even if petitioner's ongoing MS is a significant part of the explanation for her post-vaccination myelitis, petitioner need not demonstrate her vaccine to have been the sole or predominant cause of her injury. *Shyface*, 165 F.3d at 1344.

c. ***Loving*** **Prongs Five and Six**

Whereas the fourth *Loving* prong addresses general causation (*i.e*., can the vaccine in general significantly aggravate a given condition), *Loving* prongs five and six address specific causation (*i.e*., did the vaccine significantly aggravate this petitioner's

[39] In *Sharpe*, the petitioners argued that their minor child suffered a seizure disorder that was significantly aggravated by vaccination. However, the special master concluded that the seizure disorder was solely caused by a genetic mutation. *Sharpe*, 964 F.3d at 1080. The Federal Circuit assigned several errors which were ultimately interrelated. With respect to *Loving* prong three, the Circuit concluded that it was error for the special master to require petitioners to demonstrate the expected outcome of the genetic seizure disorder at issue and then prove that the child's condition was worse than that expected outcome. *Id*. at 1082. The Circuit suggested there is "a fine line between a court properly considering evidence of record and improperly placing the burden on the petitioner to prove that her significantly aggravated condition was not caused by her gene mutation." *Id.* (discussing *Stone ex rel. Stone v. Sec'y of Health & Human Servs*., 676 F.3d 1373 (Fed. Cir. 2012) (internal citation omitted).) The Circuit distinguished a prior case, *Locane v. Secretary of Health and Human Services*, on the basis that the special master in that case had considered whether the vaccine affected the petitioner's condition rather than requiring the petitioner to prove that her significantly aggravated condition was not caused by her pre-existing condition. *Id*. (citing 685 F.3d 1375 (Fed. Cir. 2012)). That analysis, in turn, informed the Circuit's treatment of *Loving* prong four.

condition). Specific causation is necessarily predicated on general causation and the attendant analysis is premised on the nature of the theory of general causation. The "did it" analysis is split between two prongs. *Loving* prong five requires a logical sequence of cause and effect and *Loving* prong six relatedly, but separately, requires a proximate temporal relationship. I start by taking timing under *Loving* prong six out of order.

i. *Loving* prong six

The sixth *Loving* prong requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Loving*, 86 Fed. Cl. at 144; *Althen*, 418 F.3d at 1281. That term has been equated to the phrase "medically-acceptable temporal relationship." *Althen,* 418 F.3d at 1281. A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan*, 539 F.3d at 1352. The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one's requirement). *Id.*; *Shapiro v. Sec'y of Health & Human Servs.*, 101 Fed. Cl. 532, 542 (2011), *recons. den'd after remand*, 105 Fed. Cl. 353 (2012), *aff'd mem.*, 503 Fed. Appx. 952 (Fed. Cir. 2013); *Koehn v. Sec'y of Health & Human Servs.*, No. 11–355V, 2013 WL 3214877, at *26 (Fed. Cl. Spec. Mstr. May 30, 2013), *mot. for review den'd* (Fed. Cl. Dec. 3, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

Here, petitioner first sought treatment on June 5, 2016, for right side weakness and numbness, which began two nights prior, *i.e.*, June 3, 2016. (Ex. 2, pp. 51, 59.) Although the initial suspicion was transient ischemic attack, after extensive further follow up, MS was eventually diagnosed. Dr. Steel opined that prior to vaccination petitioner's condition was best characterized as RIS, but that she "experienced a clinically symptomatic event in a limited time window following vaccinations." (Ex. 20, p. 3.) He indicated that following this post-vaccination myelitis, petitioner met the diagnostic criteria for MS based on this clinically isolated event. (*Id.*) Although Dr. Sriram did not agree petitioner's vaccinations were a relevant trigger, he similarly opined more generally that petitioner's "enhancing lesions suggested a recent acute [neurologic] event." (Ex. O, p. 1.) In addition to clinical symptoms, this is based on the fact that petitioner's spinal lesion grew in size from when it was first observed on June 6, 2016, to when petitioner had a second MRI on August 17, 2016. (Ex. A, p. 8.) Dr. Sriram agreed that MS-related spinal demyelination was the cause of petitioner's weakness of the arms and legs. (*Id.* at 9.) Dr. Sriram also opines that petitioner had never had a clinical attack of MS prior to her June 5, 2016, presentation. (*Id.* at 8.)

In sum, Drs. Steel and Sriram agree that prior to vaccination petitioner's MS was clinically silent and that after vaccination she suffered a clinical attack of spinal demyelination in the context of her MS that caused her to seek treatment on June 5, 2016. (Ex. 20, pp. 3, 5; Ex. 54, pp. 1, 6-7; Ex. A, pp. 7-8, 13.) Thus, the fact that petitioner suffered onset of spinal demyelination occurring on or about June 3, 2016, is essentially undisputed. (Ex. A, pp. 8-9.) June 3, 2016, was approximately 42 days

following her April 22, 2016, Tdap vaccination.[40] (Ex. 1.) Dr. Steel further opines that this constitutes a medically appropriate onset for the type of autoimmune demyelination at issue. (Ex. 20, p. 3 (opining based on petitioner's CIS occurring "in a limited time window following vaccinations").) Additionally, some of petitioner's treating physicians implicitly agreed that the timing is appropriate to implicate petitioner's prior vaccination in autoimmune demyelination, albeit in the context of suspecting a different, though somewhat related, demyelinating condition (ADEM). (Ex. 4, p. 8 (Dr. Rao); Ex. 50, p. 4 (Dr. Bidwell); Ex. 5, p. 58 (Dr. Baron), Ex. 17 (Dr. Kam-Hansen).)

Petitioner has filed literature explaining that a six-week latency is generally accepted as appropriate for autoimmunity leading to demyelination. This is based on a seminal study of GBS following 1976 and 2009 flu pandemics, but also extended to CNS demyelination and MS within the literature based on case report. (Yahel Segal, Yehuda Shoenfeld, *Vaccine-induced autoimmunity: the role of molecular mimicry and immune crossreaction,* 15 CELLULAR & MOLECULAR IMMUNOL. 586, 588-89 (2018) (Ex. 25).) Some additional literature suggests other periods of onset extending for two or more months post-vaccination may be reasonable. One piece of literature filed in the case indicates that post-vaccination TM, which again Dr. Steel considers relevant, occurs up to three months following vaccination. (Agmon-Levin et al., *supra,* at Ex. 42.) Interestingly, an epidemiologic study that examined the risk of post-vaccination relapse in MS (and found none) indicated that they restricted the study to relapses occurring within two months of vaccination, explaining that "[t]he choice of a two-month risk period in which vaccination might be considered to trigger a relapse was based on data from the literature and on expert opinion." (Confavreux et al., *supra,* at Ex. P, p. 325.) A literature review filed by petitioner indicated that, while CNS demyelination often occurs within three to four weeks of vaccination, it can also occur up to six months following vaccination. (Karussis & Petrou, *supra*, at Ex. 60, p. 7.) The latter timeframe of six months is much less persuasive given the other literature of record; however, it does underscore that the three-to-four week period cannot be taken as a hard and fast deadline. Special masters are discouraged from setting hard and fast deadlines for onset based on specific studies that do not purport to set such definitive timelines. *Paluck v. Sec'y of Health & Human Servs*., 786 F.3d 1373, 1383-84 (Fed. Cir. 2015) (stating that "[t]he special master further erred in setting a hard and fast deadline" for onset and noting that the medical literature filed in the case "do not purport to establish any definitive timeframe for onset of clinical symptoms.").

Prior cases in this Program have likewise identified the relevant temporal period for vaccine-related CNS demyelination, including MS and ADEM, as being up to about 42 days, comparing that period to the timing of adaptive immune response otherwise commonly accepted for peripheral demyelinating conditions such as GBS. *See Smith*, 2016 WL 2772194, at *18; *Quackenbush*, 2018 WL 1704523, at *20; *Robinson,* 2021

[40] In point of fact, Dr. Sriram states in his second report that onset was about 45 days following the Tdap vaccine. (Ex. O, p. 5.) However, this would refer to the date petitioner presented to the hospital rather than the date of onset of her symptoms. Dr. Sriram clearly indicated in his first report that it was the condition that led to her June 5, 20216 admission that constituted onset of her attack. (Ex. A, p. 8.) At her initial medical encounter, petitioner indicated she had been suffering her symptoms for two nights, placing onset on June 3. (Ex. 2, p. 51, 59.)

WL 2371721, at *22 (applying Langmuir's six-week (42-day) onset interval to MS and finding 13 days post influenza vaccination is a medically acceptable timeframe to infer causation given the mechanism of molecular mimicry). In fact, an onset period of up to 42 days has also been widely acknowledged in other Vaccine Program cases in a variety of other contexts in which molecular mimicry has been proffered as the causal mechanism. *See e.g., Ferguson v. Sec'y of Health & Human Servs.,* No. 17-1737V, 2021 WL 6276204 (Fed. Cl. Spec. Mstr. Dec. 10, 2021) (finding ITP onset within 30 days post Tdap vaccination is a medically acceptable timeframe to infer causation given the mechanism of molecular mimicry and O'Leary et al.'s timeframe of 1 to 42 days as the period of exposure); *Randolph v. Sec'y of Health & Human Servs.,* No. 15-146V, 2021 WL 5816271 (Fed. Cl. Spec. Mstr. Nov. 12, 2021) (finding that petitioner's Bickerstaff Brainstem Encephalitis symptoms manifested in 43 days, one day over the appropriate six-week (42-day) medically acceptable timeframe post influenza vaccination); *Koller v. Sec'y of Health & Human Servs.*, No. 16-439V, 2021 WL 5027947, at *23 (Fed. Cl. Spec. Mstr. Oct. 8, 2021) (citing "42-day timeframe" and finding GBS onset of 12 days after Prevnar 13 vaccination to be "within the medically accepted timeframe consistent with petitioner's theory of molecular mimicry [and] that has been accepted in other Vaccine Program cases."); *Barone v. Sec'y of Health & Human Servs.,* No. 11-707V, 2014 WL 6834557, at *13 (Fed. Cl. Nov. 12, 2014) ("[S]pecial masters have never gone beyond a two-month (meaning eight week) interval in holding that a vaccination caused a demyelinating illness).

Dr. Sriram, for his part, opined that the vaccinations at issue were entirely irrelevant. Accordingly, he did not specifically opine as to any temporal relationship. Notably, however, he did not otherwise raise any additional reasons why petitioner's assertion of a temporal relationship should be viewed as incorrect. To the extent he agreed that infections and withdrawing of immune modulating therapy can precipitate MS relapse, he did not identify any other relevant temporal relationship between those triggers and MS relapse. (Ex. O, pp. 6-7.) To the extent Dr. Sriram agreed that MS is likely autoimmune generally and Dr. Steel further explicitly invoked molecular mimicry, Dr. Sriram did not suggest that molecular mimicry and/or autoimmunity occur on any time course incompatible with the facts of this case. That is, Dr. Sriram did not challenge the notion that there is an apparent temporality as Dr. Steel opined.[41]

[41] For example, in his first report Dr. Sriram specifically responded to Dr. Steel's statement that the vaccines were in "close temporal proximity" to onset of petitioner's MS. He responded only that "[t]he prevailing opinion does not support the view that vaccines, even when given in 'close temporal proximity,' in any way 'trigger' onset or relapses in patients with MS, including individuals with previously clinically silent MS." (Ex. A, p. 15.) He concluded that report by indicating that "[o]ther than offering a temporal relationship between [petitioner's] receipt of the Tdap and polio vaccines and the development of clinical and new MRI lesions, Dr. Steel does not provide a biological basis on which vaccines can cause worsening of MS." (*Id*. at 16.) Thus, Dr. Sriram appears to accept Dr. Steel's assertion of temporal proximity at face value. However, contrary to Dr. Sriram's quoted statement, Dr. Steel did cite a biological basis for causation – citing well established theories of autoimmunity, including molecular mimicry – in his first report. (Ex. 20, p. 5.)

Based on all of the above, petitioner has preponderantly shown that onset of her MS attack occurred within a timeframe during which a causal relationship to her Tdap vaccination can be inferred.[42]

ii. *Loving* prong five

The fifth *Loving* prong requires proof of a logical sequence of cause and effect connecting petitioner's vaccination(s) and injury, usually supported by facts derived from a petitioner's medical records. *Loving*, 86 Fed. Cl. at 144; *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375–77; *Capizzano*, 440 F.3d at 1326; *Grant*, 956 F.2d at 1148. However, medical records and/or statements of a treating physician do not *per se* bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. *See* 42 U.S.C. §300aa-13(b)(1) (providing that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court"); *Snyder v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 746 n.67 (2009) ("there is nothing ... that mandates that the testimony of a treating physician is sacrosanct—that it must be accepted in its entirety and cannot be rebutted").

Many of the factors underlying the logical sequence of cause and effect at issue have been discussed in the preceding analyses. As explained relative to *Loving* prongs one through three, there is preponderant evidence that petitioner suffered an attack of spinal demyelination as the first clinical attack of her MS within 42 days of her Tdap vaccine. As further noted in discussion of *Loving* prong six, this much is effectively undisputed by respondent's expert in that Dr. Sriram's review of petitioner's history confirms petitioner presented for treatment on June 5, 2016, suffering a recent acute neurologic event. (Ex. O, p. 1.) I have additionally concluded pursuant to *Loving* prong three that this constituted a significant aggravation of her pre-existing MS and pursuant to *Loving* prong six that the timing is medically appropriate to infer vaccine causation. However, two issues hinder strict reliance on petitioner's medical records for any further assessment of whether a logical sequence of cause-and-effect supports vaccine-causation.

First, uncertainty regarding petitioner's correct diagnosis has obscured any direct causal opinion. Some of petitioner's treating physicians were willing to causally link her initial presentation to her prior vaccination(s); however, those physicians had diagnosed

[42]Some cases involving GBS have noted a period of up to about two months to be medically reasonable for autoimmune demyelination. *Barone*, 2014 WL 6834557, at *13. This is also consistent with at least some of the literature discussed above and would further bring petitioner's earlier polio vaccine into medically appropriating temporal proximity. However, Dr. Steel discussed the combined effects of the two vaccines. (Ex. 20, p. 5; 54, p. 7.) Thus, it is ultimately the timing of the second vaccine, the Tdap vaccine, that is most relevant. It is less obvious that petitioner would be able to prevail if her claim was based on the earlier polio vaccine alone. *E.g., Archer v. Sec'y of Health & Human Servs.*, No. 15-656V, 2021 WL 2666692 (Fed. Cl. Spec. Mstr. May 27, 2021) (noting that petitioner's expert indicated appropriate timing for post-Tdap TM to be up to six weeks and finding petitioner unpersuasive in suggesting 54-day onset is medical appropriate).

ADEM rather than MS. (Ex. 4, p. 8 (Dr. Rao); Ex. 50, p. 4 (Dr. Bidwell); Ex. 5, p. 58 (Dr. Baron), Ex. 17 (Dr. Kam-Hansen).) This difference in diagnosis makes it impossible to credit those causal opinions beyond a general recognition that onset of what they recognized as immune-mediated demyelination occurred within the timeframe for which vaccine causation of such demyelination could be inferred.[43] Those treating physicians who diagnosed MS were simply silent as to any underlying cause or trigger for petitioner's attack, providing no evidence either supporting or contradicting her claim.

Second, Dr. Steel and Dr. Sriram generally agree on petitioner's clinical history and both experts are fundamentally speaking to the same disease process. That is, regardless of whether I accept Dr. Steel's or Dr. Sriram's opinion, there is still agreement that petitioner was suffering a first clinical attack of MS and that this attack of MS constitutes inflammatory and autoimmune demyelination. This fact alone will explain virtually all of petitioner's relevant clinical findings and test results. For example, while the presence of oligoclonal bands may be important evidence of CNS inflammation in a more broadly contested case, both Drs. Steel and Sriram can claim that finding as consistent with their opinion. Neither expert discusses any test or factor, apart from personal clinical history, that can distinguish MS relapses by trigger.[44]

Important then is the fact that the record of this case does not identify any other suspected cause for petitioner's clinically isolated event based on her own clinical history. For example, although Dr. Sriram indicates that the precipitating factors for MS relapses remain unknown, he also specifically opines that infections and immune modulating therapy withdrawal can bring about a relapse. (Ex. O, pp. 6-7.) In that regard, he has not suggested that either of these factors were present in this case. Nor does my review of the medical records suggest that petitioner had any relevant prior infection or immune modulating treatment. Dr. Steel separately filed literature indicating that stressful life events can exacerbate MS (Mohr et al., *supra,* at Ex. 44); however,

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[43] As respondent notes, CNS demyelinating conditions are not interchangeable. (ECF No. 98, p. 13, n. 15.) They are, however, closely related. As discussed in the prior ruling on entitlement in addressing Dr. Kam-Hansen's causal opinion, although petitioner's correct diagnosis is MS, ADEM and MS can be difficult to distinguish upon initial presentation. (ECF No. 73, p. 18; 2021 WL 750416, at *13.) In that regard the medical records suggest that the perceived temporality to vaccination partly informed the ADEM diagnosis in this case. (Ex. 17, p. 1 (Dr. Kam-Hansen stating "[t]hese neurological findings are not unique for ADEM or MS, but the fact that there was a temporal relationship between her symptom start and the preceding vaccination, as well as the lack of any prior neurological symptoms which would suggest the presence of MS before June of 2016, means that ADEM was more likely to cause her symptoms.")

[44] For example, one paper filed by petitioner regarding MS explains that:

> There is no single diagnostic test for MS and the diagnosis is usually based on the clinical presentation, supported by neuroimaging and in some cases by CSF analysis (to look for inflammatory markers oligoclonal bands and/or elevated IgG index) and evoked potential studies (to look for clinically silent lesion in visual, brainstem, or spinal cord pathways).

(Garg & Smith, *supra,* at Ex. 45, p. 4.) CSF inflammatory markers are present in up to 85% [of] patients with MS; IgG index is less sensitive and specific than oligoclonal bands. (*Id.* (internal citations omitted).)

nothing in the record suggests that petitioner was experiencing any such event at or prior to onset of her MS. Although petitioner did have some chronic complaints unrelated to her MS, neither Dr. Sriram nor Dr. Steel has suggested that they were contributory to the specific MS attack at issue.[45]

In *Capizzano v. Secretary of Health and Human Services*, the Federal Circuit explained that:

> "A logical sequence of cause and effect" means what it sounds like—the claimant's theory of cause and effect must be logical . . . We see no reason why evidence used to satisfy one of the *Althen III* prongs cannot overlap to satisfy another prong. In other words, if close temporal proximity, combined with the finding that hepatitis B vaccine can cause RA, demonstrates that it is logical to conclude that the vaccine was the cause of the RA (the effect), then medical opinions to this effect are quite probative . . . We recognize, as the Court of Federal Claims observed, that the immense number of people receiving the hepatitis B vaccine statistically results in instances where individuals suffer an initial onset of rheumatoid arthritis shortly after receiving the vaccine, but not as the result of the vaccine. However, the statute requires only that the claimant show that it is more likely than not that *this claimant's* RA was caused by the vaccine.

440 F.3d 1317, 1326 (Fed. Cir. 2006) (emphasis original, internal citations omitted).[46]

The *Capizzano* Court reached its conclusion in light of the strength of treating physician opinions available in the case. In later cases, however, the Federal Circuit further indicated that "a petitioner is certainly permitted to use evidence eliminating other potential causes to help carry the burden on causation and may find it necessary to do so when the other evidence on causation is insufficient to make out a prima facie case." *Walther*, 485 F.3d at 1151; *see also Pafford v. Sec'y of Health & Human Servs*., 451 F.3d 1352 (Fed. Cir. 2006). The *Walther* court also explained that:

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[45] Dr. Steel did suggest that the fact that petitioner had pre-existing autoimmune disease in the form of unrelated Graves' Disease could be an additional predisposing factor, though there has been no suggestion the condition played any specific role in the onset of her clinically overt MS. (Ex. 54, p. 7.)

[46] On the other hand, the *Capizzano* Court also stated that:

> [t]he second prong of the *Althen III* test is not without meaning. There may well be a circumstance where it is found that a vaccine *can* cause the injury at issue and where the injury was temporally proximate to the vaccination, but it is illogical to conclude that the injury was actually caused by the vaccine. A claimant could satisfy the first and third prongs without satisfying the second prong when medical records and medical opinions do not suggest that the vaccine caused the injury, or where the probability of coincidence or another cause prevents the claimant from proving that the vaccine caused the injury by preponderant evidence.

440 F.3d at 1327 (emphasis original).

> [w]hen a case involves multiple causes acting in concert (*not* the situation involved here), we recognized in *Shyface* that a petitioner need not show the asserted vaccine was the predominant cause but must show that it was substantial. Where multiple causes act in concert to cause the injury, proof that the particular vaccine was a substantial cause may require the petitioner to establish that the other causes did not overwhelm the causative effect of the vaccine.

485 F.3d 1146, at n. 4 (internal citation omitted) (citing *Shyface*, 165 F.3d at 1352-53).

In this case, petitioner's satisfaction of *Loving* prongs three, four, and six, Dr. Steel's further diagnostic and causal opinion and explanation, the lack of any contradictory treating physician opinion, and the absence of any known alternative trigger, all support a logical sequence of cause and effect pursuant to *Loving* prong five. Also notable to this point is the fact that the medical event at issue was CIS, the first onset of petitioner's clinically overt MS, rather than just one relapse indistinguishable from an established pattern of relapses experienced by the petitioner. This is consistent with Dr. Steel's reliance on the "fertile field" concept of MS autoimmunity and has previously been considered a relevant factor favoring a prior petitioner's demonstration of a logical sequence of cause and effect supporting significant aggravation of MS. *Quackenbush-Baker*, 2018 WL 1704523, at *17-19. The literature filed in this case shows that most, but certainly not all, patients with RIS will go on to develop CIS and/or ultimately be diagnosed with clinically definite MS. (Okuda et al., *supra,* at Ex. 46, p. 686 (noting up to 84% of patients with RIS progressing to CIS); and Scott, *supra,* at Ex. 65, p. 375 (explaining 80-90% of patients with APTM will transition to clinically definite MS).) In that regard, the literature indicates that RIS is not destiny. Thus, when considering all of this, the sequence of cause and effect between vaccination and injury is "logical" just as the Federal Circuit noted in *Capizzano*.

To the extent Dr. Sriram opined that petitioner's MS should be viewed as the sole cause of the relapse at issue, this is not persuasive for the reasons discussed above with respect to *Loving* prong four. Dr. Steel is persuasive in presenting MS as multifactorial and MS relapses as responsive to immune stimuli. Moreover, Dr. Sriram offered no explanation of the relapsing nature of MS that could otherwise explain why petitioner's own relapse was necessarily solely attributable to the MS itself. Rather, he acknowledged that the reason for that pattern of disease is not known. Moreover, the literature filed in this case indicates that relapses are biologically "disassociated" from the neurological progression of the disease. In any event, Dr. Sriram acknowledges that at least some immune triggers do cause MS relapses, which is in tension with his underlying premise that MS alone must necessarily be viewed as the sole causal factor.

d. Factor unrelated

Based on the analysis above, petitioner has demonstrated that her MS was, in fact, significantly aggravated by vaccination by satisfying each of the six *Loving* prongs by preponderant evidence. Once petitioner has satisfied her own burden pursuant to the *Loving* test, the burden shifts to respondent to demonstrate that the injury was caused by factors unrelated to vaccination. § 300aa-13(a)(1)(B); *Deribeaux v. Sec'y of Health & Human Servs.*, 717 F.3d 1363, 1367 (Fed. Cir. 2013).

In order to meet his burden, respondent must demonstrate by preponderant evidence "that a particular agent or condition (or multiple agents/conditions) unrelated to the vaccine was in fact the sole cause (thus excluding the vaccine as a substantial factor)." *de Bazan*, 539 F.3d at 1354. As with petitioner's burden under *Althen*, respondent must show a logical sequence of cause and effect linking the injury to the proposed factor unrelated. *Deribeaux*, 717 F.3d at 1369. It need not be scientifically certain but must be legally probable. *Id*. Conditions or other factors that are "idiopathic, unexplained, unknown, hypothetical, or undocumentable" cannot defeat a petitioner's claim. § 300aa-13(a)(2); *Knudsen*, 35 F.3d at 548.

As discussed in the preceding section, Dr. Sriram has not identified any relevant alternative trigger to the specific MS relapse at issue. He urges "clinical prudence and parsimony," however, and opines that petitioner's MS itself should be viewed as the sole cause of her demyelinating attack that happened to occur post-vaccination. Specifically, he opined that "[w]hen a neurological syndrome like spinal myelitis is a well-defined part of the clinical picture of a given disease, e.g., MS, it is clinical prudence and parsimony (Occam's Razor) to recognize that the clinical picture is more than likely to be due to the underlying disease process, i.e., MS, than some other cause." (Ex. O, p. 2.) However, for all the reasons discussed within the *Loving* analysis above, Dr. Steel is persuasive in opining that the underlying etiology of MS and MS relapses are multifactorial and Dr. Sriram has not persuasively substantiated his contrary view. Additionally, as noted in the preceding section, Dr. Sriram acknowledges that at least some immune triggers do cause MS relapses, which is in tension with his premise pursuant to Occam's razor that petitioner's underlying MS necessarily constitutes the sole explanation of petitioner's post-vaccination condition. Thus, respondent does not meet his burden of preponderantly establishing that petitioner's pre-existing MS is a factor unrelated to her vaccination that solely explains her condition such that vaccination would be precluded as a substantial contributing factor.

VI. Conclusion

This case was remanded "for the Special Master to consider the parties' arguments on aggravation of MS and to re-evaluate the medical evidence under the correct legal and scientific standards." (ECF No. 90, p. 10.) The Opinion and Order remanding this case instructed that "[t]he Special Master shall issue a new entitlement decision within ninety days of this decision."[47] (*Id*.)

For all the reasons discussed above, I have completed this remand instruction and issue the instant decision on remand. On remand, I find that petitioner is entitled to compensation for a significant aggravation of her MS caused-in-fact by her April 22, 2016, Tdap vaccination. Additionally, based on the record as a whole I find that

[47] Pursuant to Vaccine Rule 28.1(a) "[i]f the assigned judge remands the case to the special master, the special master, after completing the remand assignment, must file a decision on remand resolving the case, unless the remand order directs otherwise." Pursuant to Vaccine Rule 28.1(b) "[u]nless otherwise specified in the remand order, the decision on remand constitutes a separate decision for purposes of Vaccine Rules 11, 18, and 23, i.e., judgment automatically will be entered in conformance with the special master's decision on remand unless a new motion for review is filed pursuant to Vaccine Rule 23."

petitioner is entitled to an award as stated in respondent's October 4, 2021 proffer on award of damages at ECF No. 82.

Accordingly, **I award petitioner a lump sum payment of $137,400.00**, **representing $135,000.00 in compensation for pain and suffering and $2,400.00 in compensation for past unreimbursable expenses, in the form of a check payable to Petitioner.** This amount represents compensation for all damages that would be available under § 15(a).

In the absence of any motion for review, the clerk of the court is directed to enter judgment in accordance with this decision.[48] Pursuant to Vaccine Rule 28.1(a), the clerk of court is directed to notify the assigned judge of the filing of this decision on remand.

IT IS SO ORDERED.

s/Daniel T. Horner
Daniel T. Horner
Special Master

[48] Pursuant to Vaccine Rule 11(a), entry of judgment can be expedited by the parties' joint filing of notice renouncing the right to seek review.